"A PROSPECTIVE, RANDOMIZED OPEN LABEL STUDY TO COMPARE THE EFFICACY OF TOPICAL LULICONAZOLE WITH TOPICAL TERBINAFINE IN THE TREATMENT OF TINEA CORPORIS AND TINEA CRURIS"

Dissertation submitted to

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In partial fulfilment of the regulations for the award of the degree of

M.D. (PHARMACOLOGY)

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CHENGALPATTU MEDICAL COLLEGE

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CERTIFICATE

This is to certify that this dissertation entitled, **"A PROSPECTIVE, RANDOMIZED OPEN LABEL STUDY TO COMPARE THE EFFICACY OF TOPICAL LULICONAZOLE WITH TOPICAL TERBINAFINE IN THE TREATMENT OF TINEA CORPORIS AND TINEA CRURIS"** submitted by **Dr. AMUDHA .G**, in partial fulfilment for the award of the degree of M.D.(Pharmacology) by The Tamilnadu Dr. M.G.R. Medical University, Chennai is a bonafide record of the research work done by her, under the guidance of **DR. B. SHARMILA, M.D. ,** Professor and Head, Department of Pharmacology, Chengalpattu Medical College during the academic year 2015-18 in the Department of Pharmacology, Chengalpattu Medical College ,Chengalpattu- 603 001.

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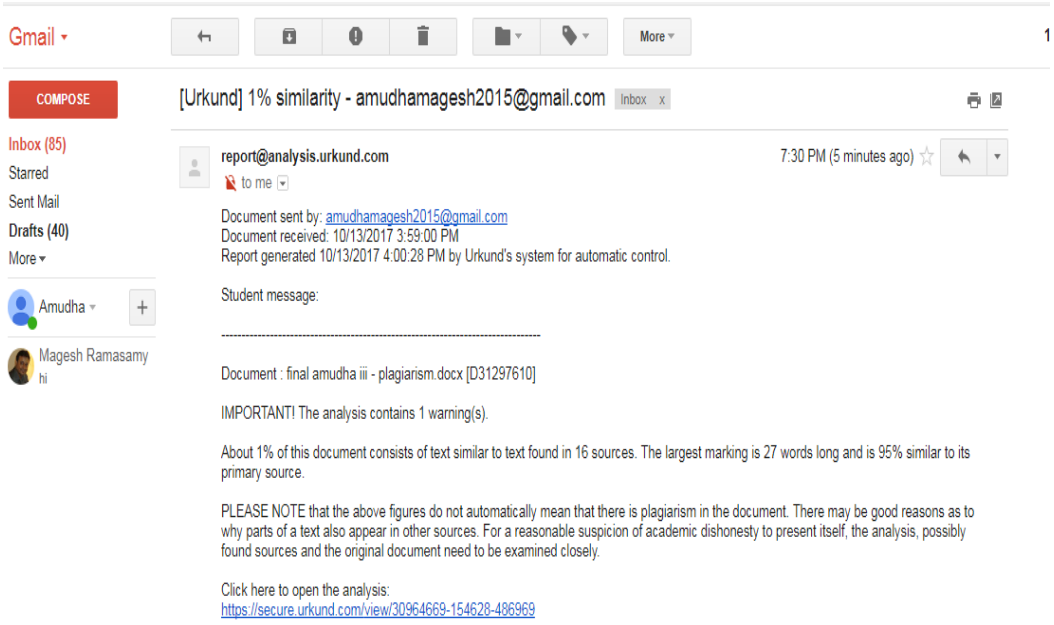

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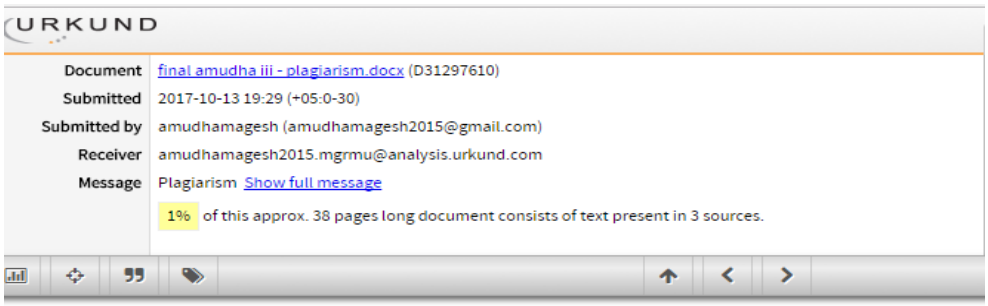

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"A PROSPECTIVE, RANDOMIZED OPEN LABEL STUDY TO COMPARE THE EFFICACY OF TOPICAL LULICONAZOLE WITH TOPICAL TERBINAFINE IN THE TREATMENT OF TINEA CORPORIS AND TINEA CRURIS" 1. INTRODUCTION Fungal infections or mycoses are common in hot and humid climate of the tropical countries like India eventhough they are capable of colonizing in any environment (1). There are approximately 1,00,000 species of fungi distributed worldwide (2). Among these fungi Tinea or Ring worm infection is caused by distinct class of fungi called dermatophytes and the infection is called as dermatophytosis. Dermatophyte infections are one of the earliest occur globally (1) and it affects 20% to 25% of the world's population. This incidence is found to be increasing progressively (2) . Clinical fungal infections are generally divided into three forms, superficial, subcutaneous, and deep/systemic. In superficial fungal infections, dermatophytosis are the most prevalent and the others are surface infections and candidiasis (3). The superficial fungal infections usually confined to the epidermis and never invade the dermis. According to Emmon's classification (4) the three genera of superficial imperfect fungi (5) having etiological importance are Microsporum, Trichophyton and Epidermophyton. Dermatophytes are the keratinophilic fungi which infect and multiply in the keratinized tissues like scalp hair, stratum corneum of the skin and nails. They synthesis and release proteases that digest keratin. Tinea corporis is dermatophyte invasion on the stratum corneum of the trunk and limb(3) and Tinea cruris is a dermatophyte infection of the groins(1). In our tropical country India, the factors such as malnutrition, poor hygienic conditions, hot and humid climate, sweating, close contact with infected persons due to overcrowding, diabetes mellitus, prevalence of immunodeficient diseases and administration of

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1. INTRODUCTION

Fungal infections or mycoses are common in hot and humid climate of the tropical countries like India eventhough they are capable of colonizing in any environment(1). There are approximately 1,00,000 species of fungi distributed worldwide(2). Among these fungi Tinea or Ring worm infection is caused by distinct class of fungi called dermatophytes and the infection is called as dermatophytosis. Dermatophyte infections are one of the earliest occur globally(1) and it affects 20% to 25% of the world's population. This incidence is found to be increasing progressively(2) . Clinical fungal infections are generally divided into three forms, superficial, subcutaneous, and deep/systemic. In superficial fungal infections, dermatophytosis are the most prevalent and the others are surface infections and candidiasis(3).

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Tinea corporis is dermatophyte invasion on the stratum corneum of the trunk and limb(3) and Tinea cruris is a dermatophyte infection of the groins(1). In our tropical country India, the factors such as malnutrition, poor hygienic conditions, hot and humid climate, sweating, close contact with infected persons

due to overcrowding, diabetes mellitus, prevalence of immunodeficient diseases and administration of steroids predispose to dermatophyte infections(7).

Drugs which are currently available for the treatment of fungal infections are enumerable. The appropriate treatment of choice is selected based on the site of infection and the type of infection. Both topical and systemic administration of antifungal drugs may be used to treat dermatophyte infections. The oral and parenteral dosage forms are indicated for systemic infections. In the treatment field, the groups of topical agents that remain as the current treatments of choice for dermatophytosis are imidazoles and allylamines.

Topical terbinafine a broad spectrum lipophilic, allyl amine drug has an excellent antifungal activity in patients with tinea corporis or tinea cruris. Topical luliconazole, an imidazole antifungal drug, has been introduced recently as a 1% cream and 5% nail solution is effective against dermatophytes and candida albicans(8). In this study an attempt has been made to assess the efficacy of topical 1% luliconazole cream in dermatophytosis in comparison with topical terbinafine 1% cream once daily application for 2 weeks and the details are elaborately discussed in the ensuing chapters.

2. REVIEW OF LITERATURE

Dermatophytosis refers to superficial infections of the skin, hair and nails due to a group of filamentous fungi called dermatophytes(10). The life-time risk of acquiring dermatophytosis is estimated as 10- 20%(10). There are approximately 40 different species of dermatophytes, of which *Trichophyton rubrum* is the most common(5). The term Dermatophytes is derived from the Greek words meaning "skin plant". While naming the infections, the word "Tinea"(Latin for "worm")[3] precedes the Latin name for the involved body site(12). Tinea corporis is synonymously called as Tinea circinata due to the circular appearance of the lesion and Tinea cruris is synonymously called as Ringworm of the groin, Dhobie itch or Eczema marginatum(4).

In tropical countries like India, living conditions are crowded with higher chances of skin to skin contact with humans as well as with close proximity to animals, poor hygienic environments or inadequate medical therapy may increase the epidemic nature of dermatophytosis. Although dermatophytosis is a less severe infection, the psychological aspects of the disease represents a major public health problem, in terms of loss of working days and requirement of expensive antifungal therapy and has become a major public health concern (14). They could survive at temperatures of 25-28°C and may reach epidemic proportions in areas having climatic conditions with higher humidity, over population and sub optimal hygienic conditions(15).

The species of dermatophytes isolated from skin lesions had shown a shift in the last 70 years. Before the Second World War in Germany, *Microsporum*

audouinii and *Epidermophyton floccosum* infections dominated , whereas *Trichophyton rubrum* is the most common dermatophyte since the fifties of last century, which accounts for 80–90% of the strains, followed by *T. mentagrophytes*(16) . Before the Second World War in Germany, *Microsporum audouinii* and *Epidermophyton floccosum* ranked the first, whereas *Trichophyton rubrum* is the most common dermatophyte since the fifties of last century, accounting for 80-90% of the strains, followed *by T. mentagrophytes*. This evolution is typical for Central and North Europe and it needs to be connected with the increase in the incidence of tinea pedis. In contrast, in Southern Europe and in Arabic countries, zoophilic dermatophytes, such as *Microsporum canis or Trichophyton verrucosum*, are the most frequently isolated organisms. In Europe, especially in Mediterranean countries, the incidence of M. canis infection has strongly increased during the recent years and this dermatophyte is now the most prevalent in tinea capitis in children. An analysis of the frequency and distribution of tinea pedis in different occupations and leisure-time activities as well as the routes of infection are reported. The spreading of this disease in most developed countries of the world represents a considerable economic problem, since it was accompanied by a parallel increase in the frequency of onychomycosis which implies, as tinea pedis, large financial charges. In poor developing countries, mycoses appear endemically, primarily in children, and their treatment often fails because of the lack of efficient antifungals. The particular epidemiological situations of dermatophytosis and

the pathogenic spectrum of dermatophytes are examined at the example of numerous countries(15).

Fungal infections of the skin are common, indicating the organisms are contagious in nature. They are found to occur when individuals often use public changing rooms and swimming pools. However, people residing in institutions with common bathroom facilities such as boarding schools and long term care hospitals also shown to have a higher than average prevalence of this disease(17).

Factors predisposing to severe, widespread or recalcitrant dermatophytosis are associated diseases like diabetes mellitus, lymphomas, immunocompromised status,Cushing's syndrome. Breaks in the skin barrier encourage dermatophyte invasion, and increased susceptibility may be inherited or related to the competency of the immune system. Eventhough the diagnosis of tinea cruris is very straightforward in some patients, the decision of treatment is sometimes difficult, because the condition may progress to an irritant allergic dermatitis, or a common intertrigo(18). Other conditions influencing dermatophyte infections include skin disorders such as Darier disease, Hailey–Hailey disease and ichthyoses that affect cutaneous barrier function(19).

An antifungal agent is considered **Ideal** if it satisfies the following characteristics(20)

- Effective at very lower doses with broad spectrum of activity, preferably fungicidal activity
- High cure rates and lower relapse rates
- Distribution to tissue is wide and is keratinophilic and lipophilic

• Short duration of therapy.

• Good safety profile; no drug interactions

When drugs are applied topically to the skin surface, they easily penetrate into the stratum corneum to either kill the fungi or inhibit their growth, thereby resulting in clinical and mycologic eradication. The availability of topical drugs that achieve relatively rapid and effective response is significant in obtaining optimal clinical outcomes.

Azole group has expanded in to huge list since the introduction of ketoconazole. Although an imidazole, the efficacy and potency against the common dermatophytes are proved to be similar or superior to terbinafine in many studies, with improved drug delivery as it does not bind much readily to keratin(21). Though both agents inhibit the growth of fungi by interfering with the synthesis of ergosterol in the cell wall, terbinafine acts at an early step in the pathway of ergosterol synthesis; while luliconazole inhibits later step and blocks the formation of ergosterol. Both classes of drugs are well known for their high efficacy against the dermatophytes(22). However the antifungal therapy is often challenged with problems like development of resistance to available drugs and non-compliance due to prolonged duration of therapy resulting in increasing relapse rates and recurrences.

In recent years, the introduction of the new antifungal agents has represented a major advance in the therapy for dermatophytes.

DERMATOPHYTOSIS:

Infections with dermatophyte have been described since ancient times and are called dermatophytosis. In 1910, Sabouraud published the current categorization in which dermatophytes are classified by genera.

Fungal infections are classified as three types depending on the extent of involvement(23) as

- Local infections, when it involves single body area,
- Invasive, when it spreads to tissues or.
- Disseminated, when organs are involved.

The dermatophytes can be classified into three ecologic groups depending on their usual habitat as,(24)

- **Geophilic species**- Present in Soil, causes sporadic infection in humans through direct contact.
- **Zoophilic species-** Occurring in animals, transmission to humans through direct or indirect contact, usually inflammatory dermatoses and sometimes may lead to suppurative, dermatosis.
- **Anthropophilic species** - Residing in human and responsible for epidemics with little inflammation. They are transmitted through fomites from person to person.

Human travel and migration, coupled with advances in antifungal therapy, have brought about changes in the geographic distribution of dermatophytes. Other important epidemiologic factors include socioeconomic status, occupation, air conditioning and the use of footwear.

PATHOGENESIS OF DERMATOPHYTOSIS(6):

The natural defense mechanisms against dermatophytes may be immunological and non-immunological. After puberty, increase in fungistatic and fungicidal long chain saturated fatty acids occur which is responsible for the innate resistance .The commensal *Pityrosporum* yeast present in the skin helps in lipolysis, and this increases the pool of fungicidal fatty acids. In addition, other factors appearing to limit the growth of fungi in stratum corneum are serum inhibitory factor, probably unsaturated transferrin, binds to iron that dermatophytes need for continuous growth and another factor identified in serum is macroglobulin keratin inhibitor that produces modification of the growth of the organism. The three processes in the dermatophyte infection are adherence, invasion and host response.

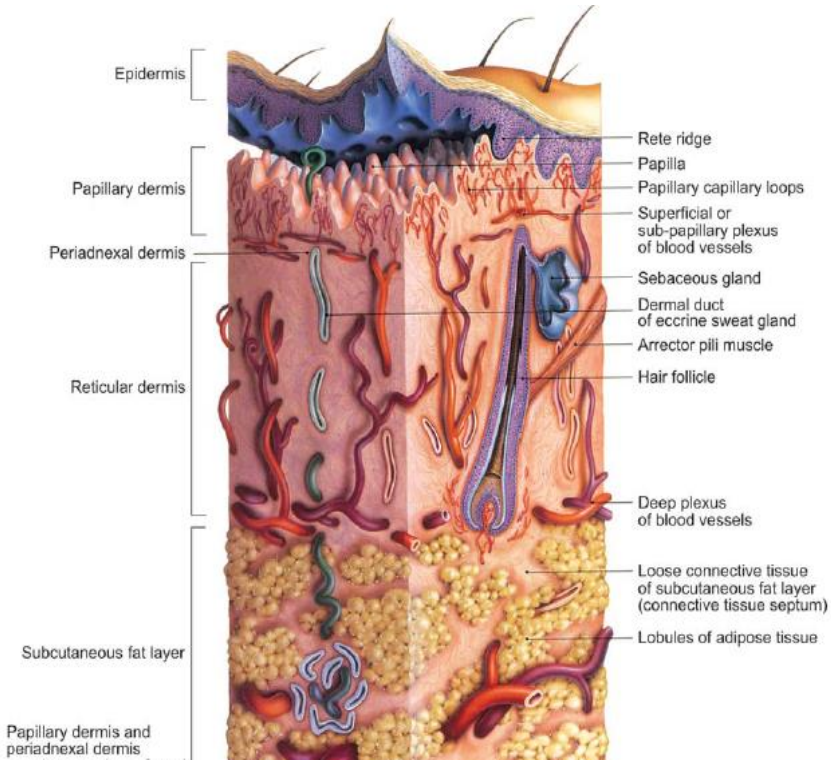


Figure 2.1 Synoptic view of cutaneous architecture

1. Adherence:

The fungal hyphae fragments to form asexual spores called arthroconidia which attach to the surface of keratinized tissues. Germination of spores occur after several hours of adherence.

2. Invasion:

Invasion is by secretion of keratinolytic enzymes like proteases, lipases and ceramidases. Keratin is degraded by these enzymes and supplies the nutrients necessary for fungal survival. Penetration through skin is facilitated by trauma and maceration.

3. Host response:

The following are the mechanisms induced by fungal invasion in the host.

A. Nonspecific Mechanisms**:**

- Secretion of fungistatic fatty acids in the sebum
- Proliferation of epidermis
- Release of proinflammatory cytokines like IFNα,TNFα,IL-1β,8,
- Secretion of antimicrobial peptides
- Increased shedding of epidermis

B. Specific Mechanisms:

The chief immunologic defense mechanism in dermatophytosis is the type IV delayed hypersensitivity reaction, a cell mediated immune response which is activated against the fungal elements resulting in clinical resolution. The

humoral immune system has a limited role in the establishment of acquired resistance to dermatophytic infections.

Different species of dermatophytes have variations in their ability to metabolize different types of keratins, e.g. *T. rubrum* never affects hair but frequently involves nails and glabrous skin, whereas *E. floccosum* never affects the hair. If a second infection by the same organism is produced in the same subject at a later stage, the site becomes inflamed very early and resolves relatively quickly.

Causative Organisms of Tinea Corporis and Tinea Cruris:

T. Rubrum and *T. Mentagrophytes* are the most common causative organisms. The distinct clinical features of different causative fungi are as follows:

Pathogens

1. *Trichophyton rubrum*: It is the most common causative agent, responsible for chronic infections. It could not survive for prolonged period of time in scale.The lesion usually extends to buttocks, waist and thighs.

2. *Trichophyton concentricum* : Typically causes tinea imbricata and responsible for eczema marginatum.

3. *Epidermophyton floccosum*: It is the common cause of "epidemics" of tinea cruris

4. *Trichophyton mentagrophytes*: Causes severe, acute inflammation and formation of pustule. It spreads rapidly and is commonly acquired from animal dander.

4.*Microsporum canis*: usually spreads from pet animals.

5.*Microsporum gypseum*: Commonly seen with occupational exposure. Inflammatory or bullous lesions are formed.

CLINICAL CLASSIFICATION OF TINEA INFECTIONS:

There exists a wide variation in the clinical presentation of dermatophyte infection. This is due to differences in the strain of the fungus involved, the size of the inoculum, the region of the body affected and the immunity of the individual.

Clinically the tinea infections are classified according to the site of body being affected as follows (6),(3)

- Tinea corporis – trunk and limbs
- Tinea capitis- ringworm of the scalp
- Tinea barbae - infection of beard in male adolescents and adults
- Tinea faciei - infection of face
- Tinea pedis - athlete's foot
- Tinea manuum, commonly "one-hand and two-feet" involved
- Tinea cruris- jock itch
- Tinea unguium - otherwise known as Onychomycosis nail involved
- Steroid related tinea, also called as tinea incognito, altered appearance of dermatophyte infection caused by topical steroids.
- Dermatophytid reactions

TABLE: 2.1 CLINICAL FEATURES OF DERMATOPHYTE INFECTIONS

DISEASE	CLINICAL FEATURES	FUNGI COMMONLY RESPONSIBLE
Tinea capitis, ringworm of the scalp	Endothrix: Spores inside the hair; Ectothrix Spores outside the hair Follicular pustules, scaling and hair loss. (Inflammatory type (kerion): Indurated, inflammatory boggy swelling with hair loss .Scarring may follow kerion.	*T.rubrum, T.mentagrophytes E.floccosum*
• Tinea unguium, otherwise known as Onychomycocis .Nail Involved	Nails thickened, crumbled distally, discoloured, and lustreless. Usually associated with tinea pedis.	*T.rubrum, T.mentagrophytes E.floccosum*
Tinea pedis, athlete's foot	Interdigital spaces on feet of persons wearing shoes. Acute: itching,red vesicular. Chronic: itching, scaling, fissures	*T.rubrum, T.mentagrophytes E.floccosum*
Tinea faciei, infection of face	Burning, itching and erythematous scaly macule with raised border, papular lesions may occur.	*T.mentagrophytes, T.rubrum, M. audouinii and M. canis. T.imbricata, caused by T. concentricum*

Tinea manuum, commonly "one-hand and two-feet" involved	Edematous, erythematous lesion. Inflammatory vesicular/dyshydrotic/eczematous form. Hyperkeratosis of the palms and Fingers, Hyperhidrosis	*T. rubrum* and *E. floccosum*
Tinea barbae, infection of beard in male adolescents and adults	Erythema, seropurulent, pustules, scaly brown macule, crusting, Perifollicular papules pustules, scarring occurs may form sinus tracts, permanent alopecia.	*T.mentagrophytes*
Dermatophytid reactions	Usually sides and flexor aspects of flexors, palms. Pruritic, vesicular to bullous lesions. Most commonly associated with tinea pedis.	No fungi present in lesion. May become secondarily infected with bacteria.
Steroid related tinea	also called as tinea incognito, raised margins are diminished, scaling is lost and inflammation is reduced. Altered appearance of dermatophyte infection caused by topical steroids.	

TINEA CORPORIS

Tinea corporis is a dermatophyte infection of the skin of the trunk and extremities, excluding the hair, nails, palms, soles and groin. The characteristic of the typical lesion is an annular (circular lesion), well defined margins advancing centrifugally, presenting with scales and often vesiculation. The center of the lesion is less scaly where organisms are cleared by the host immune response.(9). The annular appearance of dermatophyte infection is due to four-fold increase in epidermal turnover at the inflammatory periphery of the lesion in an effort to shed the organism at the inflammatory ring .Hence because of the host inflammatory response and the increased epidermal turnover lead to shedding of the organisms at the inflammatory ring. Spontaneous resolution is possible in cases with inflammatory lesions where the source is an animal infection, while it may persist for year's non inflammatory infection (e.g. caused by *T. rubrum*). In chronic infections, the hair follicle may also be affected in addition to involvement of the stratum corneum and intense itching may lead to secondary bacterial infections.

The infection usually involves the stratum corneum. It is more prevalent in tropical environments. The most common causative organism for tinea corporis is *T. rubrum* followed by *T. mentagrophytes.*The infection may spread from tinea capitis or pedis infection in the same individual, from domestic animals or from the soil. The incubation period is 1 to 3 weeks.

When the infecting organism is of zoophilic type, the lesions are commonly seen on exposed areas of the skin (the head, neck, face and arms), if

it is due to an anthropophilic organism infection usually occurs in occluded areas or in areas of trauma, mainly causing perifolliculitis of the legs in women that may be associated with leg shaving. In Indian women the lesion is most frequently seen on or below the waistline due to the typical Indian costume, i.e. saris or salwar kameez. Morphological variants other than annular lesions are eczematous annular type, crusted type, herpetiform type and plaque type.

Differential Diagnosis of Tinea Infections(11**):**

- Annular psoriasis: Scale appear scaly or grey in colour; pitting of nail present; presence of family history of psoriasis.
- Atopic dermatitis: Personal or family history of atopy; absence of active border with central clearing; lichenified lesions.
- Erythema multiforme: Target lesions; no scale; oral mucosa may be affected, acute onset;
- Fixed drug eruption: Usually single, no scales; Dusky lesions; erythematous; often associated with sulfa, acetaminophen, ibuprofen, or antibiotic use.
- Granuloma annulare: No scale, vesicles, or pustules; smooth and nonpruritic lesions; commonly affected areas are dorsum of hands or feet.
- Lupus erythematosus (subacute cutaneous): Common over Sun-exposed areas; multiple annular lesions; female-to-male ratio 3:1
- Nummular eczema: More confluent scale; central clearing is unusual.

- Pityriasis rosea herald patch: Adolescent age; a single lesion on neck, trunk, or proximal extremity; less likely to have pruritus of herald patch ; progress to generalized rash in one to three weeks
- Seborrheic dermatitis: Erythematous base covered with greasy scale; distributed over nasolabial folds, postauricular folds, hairline, eyebrows and chest; annular lesions less common.
- Candidal intertrigo: Satellite lesions; uniformly red; no central clearing; scrotum is involved;
- Erythrasma: Red-brown coloured lesion; no active border; coral red fluorescence seen with a Wood lamp examination
- Inverse psoriasis: Red and sharply demarcated; may have other signs of psoriasis such as nail pitting.

TINEA CRURIS

Tinea cruris is a dermatophyte infection of the inguinal region, involving the inner aspects of the thigh and crural folds. It is commonly called as "Jock itch."(12). Sometimes it may extend onto the abdomen and buttocks. Men are more commonly affected than women. It is commonly noticed in tropical conditions wet or tight-fitting clothing is more common in men than in women and is frequently associated with tinea pedis. Tinea cruris occurs when ambient temperature and humidity are high. Occlusion from wet or tight-fitting clothing provides an optimal environment for infection. Other predisposing factors commonly associated are diabetes, obesity and sweating.

It is characterized by presence of erythema and pruritus in the area between the scrotum and the inner thigh which may be macerated initially noticed in the inguinal folds but can spread to the thighs, perineum, buttocks, pubic region and lower stomach(24). Typical lesions are sharply delineated with a raised, erythematous, scaly advancing border which contain pustules or vesicles. The lesion may be circinate initially and later become serpiginous. It may be unilateral or become bilateral. The scrotum is usually spared, If it is involved or there are erosions or satellite pustules, cutaneous candidiasis should be considered(1). Weeping, scattered lesions may be indicative of Candidiasis(13) Older lesions can have a lichenified and leathery appearance.

Differential Diagnosis of Tinea Cruris(14):

- **Tinea cruris** - Usually occurs in male adolescents and young men; scrotum and penis not involved.
- **Erythrasma** - Uniformly brown and scaly, with no active edge, a brilliant coral red fluorescence seen.
- **Seborrheic dermatitis** - Greasy scales; scalp (dandruff), typical distribution involving nasolabial folds, hairline, eyebrows, postauricular folds and sternum, annular lesions less common.
- **Candidal intertrigo** - Uniformly red, with no central clearing; satellite lesions,
- **Psoriasis** - Silvery scale and sharp margination; pitted nails; knee, elbow, and scalp lesions.
- **Mechanical intertrigo** - Sharp edge, no central clearing or scale.

Preventive Measures to Avoid Recurrences of Tinea Cruris :

- Patients are advised to wear loose clothing,
- Avoiding prolonged exposure to moisture,
- To dry thoroughly after bathing,
- To use topical powders, to reduce weight (if obese),
- To launder the contaminated clothes and linens, and
- To treat tinea pedis if present.

DIAGNOSTIC PROCEDURES:

The diagnosis of dermatophytosis is done by a combination of clinical observations supplemented by laboratory investigation. The signs and symptoms assessed clinically, are pruritus, erythema and scaling.

The clinical assessment is done using 4 – point scale which is graded as none (0), mild (1), moderate (2) and severe (3) depending on intensity (27, 24). The percentage reduction in total mean composite score is assessed from the improvement in clinical symptoms and signs from baseline,. The response to therapy in each patient is assessed as follows(27).

Effective treatment is defined as negative microscopic findings with mild erythema / scaling (0 or 1) and no pruritus.(28).

Microscopic Examination:(29)

Some terminologies used in identifying fungi are as follows:

- Hyphae - long, filamentous fungus cells forming a branching network called mycelium

- Macroconidia - asexual large multinucleate spores produced by vegetative reproduction
- Microconidia - asexual small spores produced by vegetative reproduction
- Appearance of conidia

The clinical diagnosis of a dermatophyte infection can be confirmed (30)

- Detecting fungal elements under microscope,
- Species identification through culture,
- Histological examination of the stratum corneum or
- Observing fluorescence patterns under Wood's light examination.

Eventhough dermatophytosis are highly prevalent among the population, they are commonly misdiagnosed by primary care physicians(15),since nonfungal mimics are common. If empirically treated with a topical steroid, a mycotic lesion will worsen and that should raise the suspicion of a dermatophyte infection. Conversely, if an antifungal agent being given for a nonmycotic lesion, there will not be any improvement at all. Hence, early laboratory diagnosis is a requisite in deciding appropriate management of these infections(32). Traditionally, the diagnosis of fungal infections has been made based on light microscopy and culture-based methods.

When the diagnosis is difficult to arrive based on the clinical signs and symptoms, a potassium hydroxide (KOH) study is many a time helpful. Samples are collected from all patients clinically diagnosed as tinea corporis and

tinea cruris. Direct examination of specimens under light microscopy is done by suspending a portion of the sample in a clearing agent, KOH -10% and the fungus is visualized as branching hyaline mycelia, which frequently show arthrospore production(33). Although it is used as a quick and inexpensive bedside tool of evidence for dermatophyte infection, species identification or categorization of susceptible organisms coud not be made from microscopic examination of KOH treated sample.

All samples are cultured, irrespective of the direct microscopic observation. The scrapings are inoculated in duplicate sets into slopes containing,

a) Sabourauds dextrose agar (SDA)(34) with chloramphenicol (0.004%)/gentamicin and

b) SDA with chloramphenicol/gentamicin and cycloheximide (0.05%)(4).

One set of SDA was incubated at 37° C and second set at 25°C. All the SDA tubes are read every day for a week following incubation and twice weekly thereafter for 4-6weeks. Lactophenol cotton blue (LPCB) mount is prepared from colonies resembling mould and examined for hyphal morphology and its pigmentation, conidia morphology (microconidia and macroconidia) and its arrangements(35). Lactic acid aids in preserving the fungal structure; phenol acts as a disinfectant and cotton blue imparts color to the structures. Morphology of the isolates are observed and the causative fungus are identified.

Haley (1982) has developed a system for identifying these fungi on the basis of gross morphology. The features observed are as follows:

1. Colony observe:

The colour (e.g., white, pearly, ivory, black), consistency and topography are observed.

2. Colony reverse:

Presence or absence of pigment is noted.

3. Microscopic morphology:

Characteristics of conidia like their shape, size and arrangement are noted. Each dermatophytic genus is identified from their growth in culture by microscopy by observing under low power (10× lens) as well as high power (40× lens) of light microscope. The following features are noticed

- Organization of hyphae whether pencil shaped, spiral, pyriform, or septate
- Pattern of production of microconidia and macroconidia like tear shaped, drop like, spherical (32) .

  In *Trichophyton* species, macroconidia are rare or absent.
- *T.rubrum*: Presence of teardrop or peg shaped microconidia developed along the sides of the hyphae.
- *T.mentagrophytes*: Produces both single cigar shaped macroconidia and clusters resembling grapes of spherical microconidia.
- *Microsporum* species: Abundant large macroconidia, having rough walled, multicellular, spindle shaped structures are seen. Microconidia are scanty.

- *Epidermophyton* species: Macroconidia are characteristic and are smooth, thin, pear or club shaped with 1-9 cells. Microconidia are absent.

Other investigative measures available to identify infecting organisms are slide culture technique and agarose gel electrophoresis. Newer non culture based techniques available are polymerase chain reaction (PCR), western blot, restriction fragment length polymorphism, antigen detection tests and identification of fungal metabolites.

PHARMACOTHERAPY OF DERMATOPHYTOSIS:

History of antifungal therapy:

In 1950, Hazen and Brown developed the antifungal agent nystatin and it was named after the New York State Department of Health(36). Amphotericin B deoxycholate, a polyene antibiotic antifungal, was introduced in 1958. Eventhough it is having wide spectrum of activity, this preparation is associated with significant renal toxicity and infusion reactions.

In 1973 Flucytosine, a pyrimidine analogue was introduced, which is effective against Candida and Cryptococcus but its use is restricted due to emergence of drug resistance and toxicity.

The first-generation azole drugs were introduced in the 1990s e.g. fluconazole and itraconazole and inspite of having higher efficacy against dermatophytes and yeast pathogens they still have the demerit of occurrences of many drug–drug interactions. Lipid-based amphotericin B formulations with less toxicity were introduced in the 1990s. The second-generation of azole drugs,

including voriconazole, posaconazole, and isavuconazole, and echinocandin drugs were brought in to market in the 2000s and offer excellent antifungal activity.

Both topical and systemic administration of antifungal drugs may be used to treat dermatophyte infections and multiple drugs are also available. The appropriate treatment of choice is selected based on the site of infection and the type of infection.

CLASSIFICATION OF ANTIFUNGAL DRUGS:

The antifungal drugs are categorized according to their mechanisms of action, as well as on their structural basis.

Classification based on the mechanisms of action:

1. Inhibitors of fungal membrane stability: e.g. Amphotericin B (AMB), Nystatin,

2. Ergosterol synthesis inhibitors:

- By inhibiting 14-α-lanosterol demethylase – e.g. Imidazoles and triazoles
- By inhibiting squalene epoxidase e.g. Allylamines.

3. Nucleic acid synthesis inhibitors; e.g. Flucytosine.

4. Inhibits mitosis by acting on the microtubules: e.g. Griseofulvin.

5. Cell wall synthesis inhibitors (inhibit formation of glucans): e.g. Echinocandins

Classification Based On Their Structural Basis: (37)

1. **Antifungal Antibiotics:**

a) Polyenes antibiotics: Amphotericin B (AMB), Nystatin, Hamycin

b) Heterocyclic benzofuran; eg. Griseofulvin

c) Echinocandins: Caspofungin, micafungin and anidulafungin

2. Antimetabolite: Flucytosine (5-FC)

3. Azoles

a) Imidazoles:

- Used only Topically: Clotrimazole, Econazole, Miconazole, Oxiconazole,
- Both topical and Systemic: Ketoconazole

b) Triazoles:

- Used only systemically: Fluconazole, Itraconazole, Voriconazole, Posaconazole

4. Allylamine:

Both topical and Systemic: Terbinafine Benzylamines : Butenafine

5. Other topical agents:

Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Butenafine, Sodium thiosulfate

MECHANISM OF ACTION OF DIFFERENT ANTIFUNGAL AGENTS:

(38)**,**(10)

The molecular targets of antifungal agents include enzymes or molecules involved in the synthesis of cell membrane, stability of cell membrane, mitosis and nucleic acid synthesis.

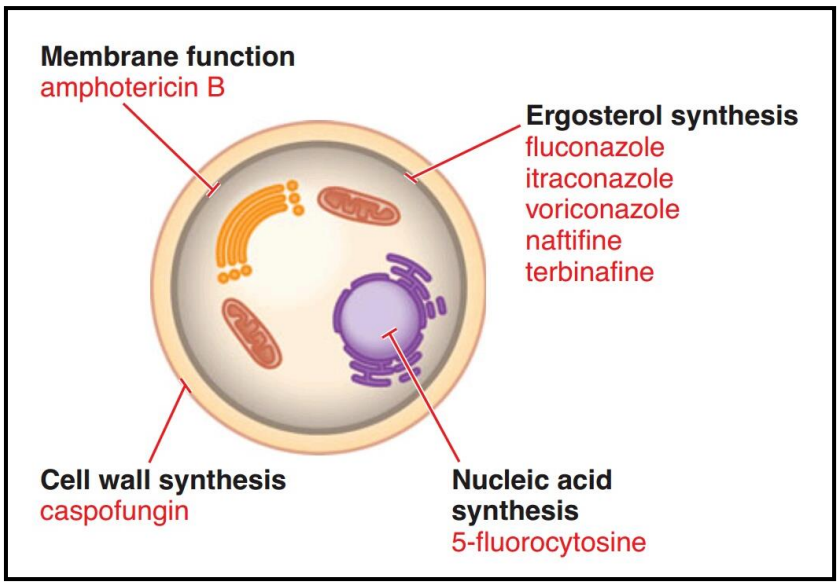


Figure 2.2 Mechanism Of Action of various antifungal agents (26)

- Azoles have combined characteristics like strong effectiveness with a relatively low incidence of secondary side effects these derivatives are considered as the most promising group in terms of antifungal therapy, as they combine. Azoles, imidazoles and triazoles inhibit the ergosterol synthesis pathway in the endoplasmic reticulum.They have also been reported to inhibit membrane-surface enzymes and lipid biosynthesis. Systemic azoles include miconazole, ketoconazole (imidazoles), itraconazole,fluconazole, terconazole, voriconazole, posaconazole,isavuconazole and ravuconazole (triazoles). Topical imidazoles are bifonazole, butoconazole, clotrimazole, econazole, fenticonazole, ketoconazole, miconazole, oxiconazole, sulconazole, tioconazole, luliconazole, and topical triazoles include efinaconazole **(**First topical triazole), and terconazole. Sertaconazole is unique in its fungicidal action unlike other azoles which are fungistatic and has additional anti-inflammatory and anti-itch properties.(39) Imidazoles are

more toxic on systemic administration and thus most of them are used topically while triazoles are less toxic, hence used by systemic route.

- Polyenes include amphotericin B, nystatin (both oral and systemic) and hamycin and natamycin (only topical). They increase the permeability of the plasma membrane. They have affinity for fungal membrane sterol moiety, resulting in the formation of aqueous pores or channels through which efflux of essential small cytoplasmic materials occurs and causes cell death.(40) Oxidative damage may also contribute to antifungal action.
- Allylamines are naftifine (topical), terbinafine (both topical and systemic), the related benzylamine butenafine) and thiocarbamates (tolnaftate and tolciclate) inhibit the enzyme squalene epoxidase which converts squalene to 2, 3-oxidosqualene. This enzyme blocks ergosterol biosynthesis, which is toxic to fungal cells.

  Griseofulvin (systemic) causes disruption of the mitotic spindle by interacting on polymerized microtubules and causes the production of multinucleate cells, eventually resulting in inhibition of fungal mitosis. It is a heterocyclic benzofuran fungistaticantifungal antibiotic.
- Ciclopirox olamine (topical) interferes with amino acid transport across the fungal cell membrane causes membrane instability by concentrating inside fungal cells exerting fungicidal and fungistatic action.
- Echinocandins are semisynthetic lipopeptides that acts possibly by competitively inhibiting β-glucan synthetase; thereby inhibiting the synthesis of β 1,3-glucan, a major structural polymer of the cell wall and

inhibit fungal cell wall synthesis(25) It is fungicidal against candida and: fungistatic against *Aspigillus*(36).

- Used systemically only. Cilofungin was the first echinocandin but it was highly toxic, hence clinical trial was withdrawn and abandoned in the 1980s.(27) eg. Caspofungin, micafungin and anidulafungin.
- Flucytosine, chemically a 5-FC, is a fluorinated pyrimidine, is converted into 5-fluorouracil which is again converted into 5-fluoro uridylic acid by the enzyme uridine monophosphate pyrophosphorylase. Subsequently, the 5-fluorouridylic acid formed is incorporated into the RNA, or may be converted to 5-fluoro deoxy uridylic acid, which inhibits the enzyme, thymidylate synthetase and ultimately DNA synthesis is inhibited as well as faulty RNA synthesis occurs.
- Morpholines (amorolfine,topical) inhibit sterol reductase and C-8 sterol isomerise, enzymes involved in the ergosterol biosynthetic pathway.(41) It is a potent fungistatic and fungicidal agent.
- Miscellaneous topical drugs include haloprogin, ciloquinol (iodochlorhydroxyquin), whitfield's ointment, castellani's paint, gentian violet, compound undecylenic acid, potassium permanganate, sodium thiosulfate, selenium sulfide, zinc pyrithione, and propylene glycol.(42)
- Newer antifungal agents include sordarins (GM193663 and GM531920) inhibit protein synthesis by interfering with the function of fungal translation Elongation Factor 2 (EF2). Since they are highly toxic, their derivatives are yet to be developed. Pramiconazole is another new

member of triazole group under development for the treatment of superficial infections caused by dermatophytes and yeasts.(10) Pradimicins are unique mechanism of action that act through calcium binding to mannans in the fungal wall and exerts antifungal effect.(43)

Systemic therapy for superficial dermatomycosis:

Systemic therapy is usually indicated in the indicated for tinea corporis involving extensive skin lesion, immunosuppressive conditions, recalcitrant lesions due to development of resistance to topical antifungal therapy, and associated with tinea capitis or tinea unguium or when the infection involves hair follicles, such as Majocchi granuloma. Topical antifungal treatment is indicated in tinea of glabrous skin, except in cases of extensive, multiple or recurrent lesions, or immunocompromised patients. However, in daily practice there are cases resistant to topical treatment despite these indications. Parasitism of the hair could be the cause behind the majority of isolated lesions of ringworm of hairless skin with a poor outcome with topical antifungal treatment.

In tinea of glabrous skin with low response to topical antifungal treatment we must rule out tinea of the vellus hair. Infection by non anthropophilic dermatophytes, previous corticosteroid therapy and excoriation might be predisposing factors. Parasitism of the vellus hair, observed by direct microscopy, should be another criterion for establishing systemic treatment from the onset, as is the case in tinea capitis (43).

Potential drug interactions are common with the use of oral agents requiring attention and monitoring for adverse effects. The preferred treatment

for tinea imbricata is griseofulvin or terbinafine, although some resistance has developed to oral griseofulvin. A dose of 10 mg/kg/day is effective. It is the systemic drug of choice for tinea corporis infections in children. In addition, griseofulvin is an enzyme inducer, hence enhances the metabolism of warfarin and oral contraceptives and therefore may cause loss of anticoagulant effect and contraceptive failure respectively. It also has disulfiram like action with alcohol. Oral terbinafine may be used at a dosage of 250 mg/day for 2 weeks; the potential exists for cytochrome P-450, specifically CYP- 2D6, drug interactions with this agent.

Systemic azoles eg, fluconazole (50-100 mg/day or 150 mg) once weekly; itraconazole (100 mg/day); ketoconazole (3-4 mg/ kg/day) function similar to the topical agents, causing cell membrane destruction. Due to inhibition of CYP 3A4 cytochrome P-450 enzyme, the concentration of phenytoin, digoxin, warfarin, sulfonyl ureas, statins, and benzodiazepines. Protease inhibitors increase the concentration of azoles whereas enzyme inducers, rifampicin reduces the concentration of azoles. Ketoconazole is nowadays replaced by other antifungals, due to its slower response, inhibitory effect on steroidogenesis and hepatotoxicity.

Voriconazole and posaconazole have extended spectrum of antifungal activity against aspergillus and candida, while the latter drug has additional activity gainst zygomycosis and mucormycosis for which till date only amphotericin B is available. Voriconazole is extensively metabolized in liver, hence dose reduction is needed in cases of hepatic insufficiency.

Flucytosine produces leucopenia and thrombocytopenia due to bone marrow suppression. Infusion reactions are common with echinocandins.

Duration Of therapy:

The oral antifungal therapy may be given either daily as continuous therapy or as pulsed therapy (1 week per month is considered one pulse). For onychomycosis for finger nails, oral itraconazole can be given as 200mg/day daily for 2 months (44)

Treatment for tinea corporis/tinea cruris:

Tinea corporis:

- Topically 2% miconazole cream or 1% clotrimazole cream or 2% ketoconazole cream or econazole cream or 1% Terbinafine cream twice daily for 1 week. Topicals should be continued for 7–14 days beyond symptom resolution.
- Systemic therapy includes oral micronized Tab. Griseofulvin (10 to 20 mg/kg) 500 mg per day or ultramicronized (5 to 15 mg/kg) 330-375 mg per day for 2-4 weeks or Tab. Itraconazole 100 to 200 mg per day(3 to 5 mg / kg per day) for one week or Tab. Fluconazole 150–300 mg (6 mg/kg) once a week, should be repeated for 4–6 weeks or Tab.Terbinafine 250 mg per day for 2-4 weeks.(24)
- The effective regimens for children are terbinafine 3–6 mg/kg/day for 2 weeks, itraconazole 5 mg/kg/day for 1 week, and ultramicro size griseofulvin 10–20 mg/ kg/day for 2–4 weeks.(6)

Tinea cruris:

- Topical econazole cream b.i.d. or 2% miconazole cream b.i.d or 2% ketoconazole cream b.i.d or 1% terbinafine cream b.i.d or 0.77% ciclopirox cream b.i.d for 2–3 weeks and should be continued for 7–14 days beyond symptom resolution.
    - Systemic therapy: Tab. Griseofulvin 500 mg o.d. for 2–4 weeks or Tab. Itraconazole 200–400 mg o.d. for 1 week or Tab. Fluconazole 150–300 mg × 1 dose, repeated for 4 weeks or Tab.Terbinafine 250 mg o.d. for 10 days.

Topical Antifungal Agents(45)**:**

In most cases of infection, management with topical antifungals is sufficient to cause desired effect; These are relatively cheaper than oral medications, minimal drug -drug interactions and cause minimal adverse effects also(20). Adherence to topical treatment is considered superior to that for oral therapy because most topical therapies are used for the reduction of symptoms in highly symptomatic disease.(47) Their main disadvantage is in patients with extensive lesions, there exists a difficulty in application of these creams/lotions to such wide body areas. Tinea corporis and tinea cruris show a very good response to topical creams such as terbinafine, but oral antifungal drugs may be indicated for extensive involvement, failed topical treatment and in immunocompromised patients(12). Topical therapy is usually preferred for uncomplicated tinea corporis and cruris of smaller areas involvement and of

shorter duration of disease.(10) . For cutaneous application, the preferred formulation is usually a cream or solution.

The effectiveness of topical antifungal agents depends on the following factors:

- Mechanism of action of the drug
- Type of lesion
- Viscosity, hydrophobicity, acidity of the formulation and
- Penetration of topical drugs into hyperkeratotic lesions. Removing the thick, infected keratin is considered as adjunct therapy along with topical agents.

Indications for topical antifungal therapy

It is highly effective in superficial fungal infections involving stratum corneum, squamous mucosa and cornea. It is useful in treating uncomplicated tinea corporis, tinea cruris, tinea versicolor, candidiasis, piedra, tinea nigra, and fungal keratitis. It could be used in limited tinea pedis and is not effective in treating severe tinea of the nails (onychomycosis), tinea capitis and subcutaneous mycoses (sporotrichosis and chromoblastomycosis). Topicals are generally applied for twice daily. The most commonly observed adverse reaction is irritant contact dermatitis, usually from the alcohols or other components in the vehicle or occasionally allergic contact dermatitis may be observed clinically.

Development of resistance to antifungal agents:

Dermatophytosis imposes significant disturbances in social, psychological, and occupational health effects and can affect the quality

of life. Early diagnosis and initiation of treatment is essential to minimize morbidity and reduces possibility of transmission. Duration of therapy is also generally long and expensive. Incomplete treatment may be frequently encountered with relapses. Recently, drug resistance could be an important problem in patients resulting in clinical failure(10).

The development of resistance to these drugs may be due to relatively increased use, inappropriate prescribing because of improper diagnosis and over the counter sale of antifungal combinations.

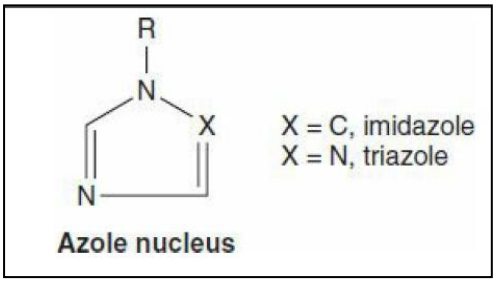
TOPICAL ANTIFUNGAL AGENTS EFFECTIVE IN DERMATOPHYTE INFECTIONS:(1)

- Ciclopiroxolamine has broad spectrum activity with fungicidal action. It inhibits the uptake of precursors of macromolecule from cell membrane which are essential for growth of fungi. Cure rate of 80% was observed in the treatment of tinea corporis, tinea cruris and pityriasis versicolor.
- Haloprogin is a halogenated phenolic ether, not preferred nowadays due to its higher incidence of irritation, pruritus, sensitization or exacerbation of the lesion during therapy.
- Tolnaftate is a thiocarbamate, less effective in thick or hyperkeratinized lesions due to poor penetration in to skin.
- Naftifine and butenafine are benzylamine congener, mechanism of action similar to terbinafine

- Benzoic acid is a weak fungistatic which is often used in combination with salicylic acid (Whitfield ointment: Benzoic acid 6% and salicylic acid 3%). Since salicylic acid is having keratolytic action, it helps to remove the infected tissue in the hyperkeratotic lesion and facilitates penetration of benzoic acid into the fungal infected tissue.
- Nystatin, a polyene drug , binds to the cell membrane constituent, ergosterol and forms pore through which Na^+, K^+, Mg^+, H^+ ions and other macromolecules to leak out of the cell causing cell death. Though the toxicities of nystatin are severe, least quantity is absorbed following topical administration to produce adverse effects.
- Quiniodochlor: otherwise called iodochloro hydroxyquin, Ciloquinol.

AZOLES:

Chemistry(38)



Azole nucleus

The availability over the past 2 decades of the azole antifungal agents represents a major advance in the management of fungal infections. Miconazole was the first azole drug to be approved(48).

They are synthetically derived compounds and the azole nucleus is a five membered ring with nitrogen atoms. Depending upon the number of nitrogen atoms they are classified into two groups, Imidazoles and triazoles.

- Imidazoles have 2 nitrogens in their azole nucleus
- Triazoles have 3 nitrogen atoms.

SPECTRUM OF ACTIVITY(17)

Highly susceptible organisms are(38)

- Candida species like *Candida albicans, Candida tropicalis, Candida parapsilosis, Candida glabrata*
- Dermatophytes
- *Blastomyces dermatitidis,*

Resistant (49)

Candida krusei and Mucormycosis.

TOPICAL IMIDAZOLES AND TRIAZOLES:(49)

Imidazoles and triazoles are closely related classes of drugs are synthetic antifungal agents that they could be used both topically and systemically. Topically they are used against ringworm, tinea versicolor, and mucocutaneous candidial infections. Resistance to imidazoles or triazoles is not so common among ringworm diseases. The suitable topical agent is selected depending upon cost and availability, because testing *in vitro* fungal susceptibility to these drugs could not predict clinical outcomes. The cutaneous preparations are not useful for oral, vaginal, or ocular infections.

Mechanism of action of azoles in the fungal cell wall(33)

The important biochemical difference between mammalian cells and fungal cell wall is the presence of ergosterol in fungi whereas cholesterol is present in the mammalian cells. The fungal cell wall is made up of chitin which

is composed of ɛtyl glucosamine and this chitin confers rigidity to the cell wall. Whereas most bacteria contain peptidoglycan in its cell wall(50). Understanding these biochemical differences in the cell structure helps in the development of antifungal drugs. In the fungal cell, acetyl CoA forms the building block for the synthesis of ergosterol. Acetyl coA is converted into intermediates like HMG coA, mevalonate and squalene. Squalene, is converted by the action of squalene epoxidase to lanosterol. This step is inhibited by allylamines and benzylamines. Lanosterol is converted by 14 α – Lanosterol demethylase to ergosterol, the important sterol of the fungal cell membrane. This step is inhibited by imidazoles and triazoles group of drugs.

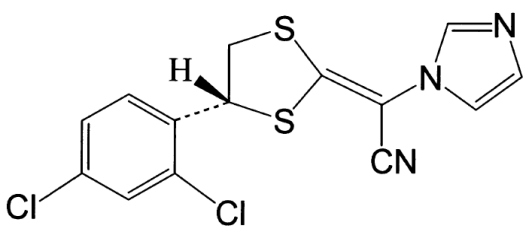
LULICONAZOLE (LLCZ):

Description:

Luliconazole was initially approved in the year 2005 in Japan for treating tinea infections(52).The LLCZ 1% cream was approved In June 2009, for marketing in India. Later it got approval by US food and drug administration in november 2013, for treating interdigital tinea pedis, tinea corporis and tinea cruris in patient's ≥ 18 years of age.

Chemical name is (2e)-2-[(4r)-4-(2, 4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-2-(1h-imidazole-1-yl) acetonitrile.

Structural formula(2**):**



Molecular weight: 354.28 gm/mol

Molecular formula: C14H9C12N3S2.

Active form of LLCZ is the R- enantiomer and has one chiral center. The double bond next to the dithiolane group is within the E configuration. The addition of imidazole moiety into the ketene dithioacetate portion of the compound confers increased effectiveness against filamentous fungi such as dermatophytes(53). The chemicals derived from this ketene dithioacetate structure has demonstrated several bioactivities like treating rice blast disease, certain hepatic disorders in human and livestock(54).

Luliconazole Cream, 1% is composed of 10 mg of luliconazole per gram of cream, present in a vehicle consisting of benzyl alcohol, isopropyl myristate, medium-chain triglycerides, butylated hydroxytoluene, cetostearyl alcohol, propylene glycol, methylparaben, polysorbate (60), purified water, and sorbitan mono stearate.

M**echanism of Action:**

They are predominantly fungistatic but fungicidal efffect is seen only at very high concentrations. Azoles selectively inhibit the enzyme 14 α lanosterol demethylase a cytochrome P-450 dependent enzyme thereby inhibiting the conversion of lanosterol to ergosterol.(36) The depletion of ergosterol, an essential component of fungal cell membrane and accumulation of 14- a-methylated sterols interferes with the function of ergosterol, causes increased

permeability and rigidity of fungal cell membrane, and disrupts the enzymes bound to fungal cell membrane, inhibiting fungal growth and replication. The selectivity to fungal cells is because human cell demethylation is much less sensitive to the inhibition of azoles.

They also interfere with the synthesis of triglycerides and phospholipids, leading to increased levels of toxic free radicals like hydrogen peroxide inside the fungal cell, eventually resulting in disruption of subcellular organelles and cell death. Their effectiveness against superficial infections caused by candida is better when compared with allylamines, because of their ability to inhibit the transformation of blastospores of Candida albicans into the invasive mycelial form(53).

Pharmacokinetics

Luliconazole is > 99% protein bound in plasma. Studies have shown that therapeutic doses of luliconazole do not inhibit cytochrome P450 (CYP) enzymes 1A2, 2C9 and 2D6 in in-vitro, but weakly inhibits the activity of CYP2C19. When luliconazole 1% Cream was applied once daily in patients with tinea cruris, the pharmacokinetics was studied and the maximum plasma concentration C(max) thus obtained was 4.91±2.51 ng/dl after the first dose and 9.36±2.66 ng/dl following the final dose. The time (Tmax) to reach the C(max) was found to be 21.0± 5.55 hours after the first dose and 6.5± 8.25 hours after the final dose(53).

Antimicrobial action:

It has been found to have strong in vitro antifungal activity against *Trichophyton spp.*, *E. floccosum*, *Candida. albicans*, and *Aspergillus fumigatus*. The antifungal activity of luliconazole was extremely high against *Trichophyton spp*. when compared to other topical antifungal drugs currently available. *Trichophyton rubrum* was found to be the most susceptible organism. The duration of therapy required to eradicate experimentally-induced *T. mentagrophytes* infections for luliconazole 1% is also half the time or less required for 1% terbinafine cream(53). The anti-Malassezia activity of LLCZ has been found to be comparable to or stronger than that of ketoconazole and this has been used clinically to treat Malassezia infections, such as pityriasis versicolor. Furthermore, in vitro potency of LLCZ against Malassezia restricta, was demonstrated to be high, hence clinically useful in the treatment of seborrheic dermatitis(54).

Dosage and administration:

It is applied to the affected skin and approximately 1 inch of the immediate surrounding area(s) once a day for one week to two week in tinea corporis/cruris and for 2 weeks in tinea pedis in patients above 18 years of age and older. It is not recommended for ophthalmic, oral or intravaginal use.

Dosage formulation available:

Each gram of 1% Cream contains 10 mg of luliconazole in a white cream base.

5% nail solution is also available for nail infections(55)

Adverse effects:

The most common adverse reactions reported were application site reactions, which were noticed in less than 1% of subjects(56). Contact dermatitis and cellulitis have occurred in the post marketing studies.

Use in specific populations:

Categorized as C in pregnant women. It is not known whether luliconazole is excreted in human milk. Safety was not established in pediatric patients.

Long-term studies are not yet conducted to evaluate the carcinogenic potential of luliconazole Cream, 1%.

ALLYLAMINES:

In 1974, Naftifine was reported to be the first synthetic allylamine antifungal drug and in 1985, it was the first commercially available allylamine in the market. It was synthesised from heterocyclic spiro-naphthalenones by acid hydrolysis(57). Then, terbinafine (SF 86-327) was developed by modification of naftifine and became the second allylamine with significant antimycotic effect. Both these antifungals have a nitrogen atom having a neighboring double bond.

TERBINAFINE:

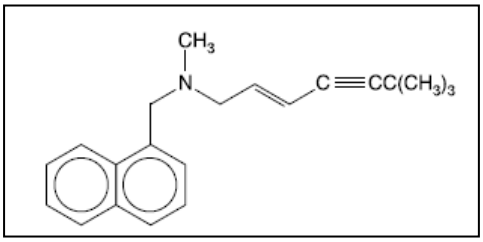
Chemical Names: Terbinafine hydrochloride; Terbinafine HCl; 78628-80-5.

Molecular Formula: $C_{21}H_{26}ClN$

Molecular Weight: 327.896 g/mol

(E)-N,6,6-trimethyl-N-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine;hydrochloride(23)

Structural formula:



Mechanism of action:(58)

Terbinafine (TFB) exerts a primary fungicidal action against dermatophytes, other filamentous fungi, and *S. schenckii*(59). The drug can act as both fungicidal and fungistatic, but it depends on the species against which it acts. Among yeasts, it can be primarily fungicidal against *Candida parapsilosis* or fungistatic, against *Candida albicans*(60). The fungicidal action is thought to result from a combination of sterol deficiency as well as heavy intracellular accumulation of squalene(29). The ratio of concentration of terbinafine required to inhibit fungal ergosterol synthesis compared with that required to inhibit mammalian cholesterol synthesis is 4000:1. This accounts for its more selectivity towards fungal cell(19).

Pharmacokinetics:

Absorption:

70% to 80% of the drug orally administered drug is well absorbed orally. > 99% of the drug is plasma protein bound. Drug is concentrated in skin, nails, and fat. The t1/2 is ~12 hours initially but at steady state it extends to 200-400 hours. Contraindicated in azotemia patients and hepatic failure. Bioavailability is ~40% due to high first-pass metabolism in the liver(18).

Drug interactions:

Being lipophilic, topical terbinafine binds strongly to the stratum corneum and penetrate into hair follicles. When the drug is applied over the skin for 7 consecutive days, plasma levels exceeding cidal concentrations are present even 7 days after discontinuation of therapy. Hence short-duration therapy is sufficient for cure(42).

Rifampicin decreases plasma levels by inducing the enzyme cytochrome P450 and cimetidine increases its levels in plasma by inhibiting its metabolism by cytochrome P450. Break through bleeding has been reported when taken together with oral contraceptives.

Adverse effects:

After topical application , only less than 5% of the drug is absorbed into the systemic circulation, hence the drug or its metabolites will not accumulate inside the body(62).Adverse effects like local burning, , dryness, pruritus, and erythema may occur in 2% of patients who applied for 1 to 4 weeks. This incidence is similarly noticed with placebo treatment.

Gastrointestinal disturbances like diarrohea, dyspepsia, and nausea, headache, rash and mild abdominal pain are the most common adverse effects after oral administration. Taste disturbances may occur and it may be associated with tongue discoloration. Rare occurrences of fatal hepatotoxicity have been reported. Severe neutropenia, and severe skin reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis, severe utricaria, pityriasis roea, worsening of preexisting psoriasis and lupus erythematosis have occurred rarely(30). There

exists a higher frequency of occurrence of erythema multiforme when compared to those with trimethoprim, sulfamethoxazole and ampicillin. All adverse events are reversed on withdrawal of the drug(50). Ocular changes like reversible green vision (Dyschromatosia), changes in lens and retina have been reported. Local reactions occur on topical use.

Antimicrobial action:

Terbinafine has broad spectrum of antifungal activity having fungicidal action against dermatophytes and also active against *Sporothrix schenckii* , some *Aspergillus* species and *Histoplasma capsulatum*[28]. When combined with fluconazole or itraconazole , it has additive and synergistic effects against *Candida Albicans* strains, *Scedosporium prolificans* and against the protozoa, *Leishmania braziliensis(*9). The drug is pregnancy Category B

Therapeutic uses:

Dosage for Oral therapy:

For onychomycosis: 125 – 250mg tablet once daily for 6-12 weeks. Also effective in tinea capitis. Oral preparations have shown effectiveness in certain non-dermatophyte infections like Aspergilllosis, Chromoblastomycosis, Candidal nail infections and sporotrichosis(23).

Topical Terbinafine:

Available as cream and spray Terbinfine hydrochloride 1% cream is applied once or twice daily for one to two weeks for the treatment of tinea corporis and tinea cruris. It is applied for one week for tinea paedis. It is also found to be useful in the treatment of cutaneous candidiasis and tinea versicolor.

Table 2.3 Comparison of minimum inhibitory concentrations of (MIC) of luliconazole and terbinafine against dermatophytes and Candida albicans.

	LULICONAZOLE	TERBINAFINE
Trichophyton rubrum	**0.00024**	**0.0078**
T.mentagraphytes	**0.002**	**0.016**
T.tonsurans	**0.0049**	**0.0078**
Candida albicans	**0.13**	**4**

The low MICs exhibited by luliconazole may be important in its clinical efficacy and low relapse rates for dermatophyte(56). Thus LLCZ is capable of eradicating fungi at a much lower concentration than that necessary for terbinafine and also completely eradicated the fungus in half or less of the treatment time required for 1% terbinafine cream, as determined by a culture assay. These results clearly indicate that 1% luliconazole cream when compared to existing drugs is sufficiently potent for short-term therapy for dermatophytosis.

3. AIM AND OBJECTIVES

3.1 AIM:

To compare the efficacy and safety of luliconazole 1%topical cream with terbinafine 1% topical cream against tinea infections.

3.2 PRIMARY OBJECTIVE:

To evaluate and compare the efficacy of terbinafine 1% topical cream group with luliconazole 1% topical cream against tinea infections

3.3 SECONDARY OBJECTIVE:

To compare the safety and tolerability of terbinafine 1% topical cream group with luliconazole 1% topical cream group in the treatment of tinea corporis and tinea cruris.

4. MATERIALS & METHODS

4.1 MATERIALS

4.1.1 DESIGN OF STUDY:

A prospective, randomized, open label, comparative study.

4.1.2 PERIOD OF STUDY:

Total 4 weeks (2 weeks therapy + 2 weeks follow up)

- Drug Administration – 2 weeks
- Post drug administration and follow up -2weeks

4.1.3 DURATION OF THE STUDY:

- December 2015 to September2017 (22months)

4.1.4 STUDY CENTRE:

- OPD, Department of Dermatology,
- Chengalpattu medical college and hospital.

4.1.5 STUDY POPULATION:

All patients attending to the dermatology outpatient department with history & clinical features of Tinea cruris and Tinea corporis fulfilling the selection criteria.

4.1.6 SAMPLE SIZE:

- 120 patients.

4.1.7 DRUGS USED AND ITS DOSAGE FORMS:

The drugs Terbinafine 1% topical cream given to group A and luliconazole 1% topical cream given to group B. Both are applied to the affected skin approximately 1 inch of the immediate surrounding area(s) once a day for two weeks.

4.1.8 ETHICAL COMMITTEE CLEARANCE:

Institutional ethical committee clearance was obtained.

4.1.9 SELECTION CRITERIA:

4.1.9.1 INCLUSION CRITERIA:

- Age: 18- 75 years
- Both gender.
- Patients with clinical diagnosis and mycological diagnosis of tinea corporis and tinea cruris by microscopic KOH wet mount
- No history of systemic illnesses.
- Patients who are willing to give informed consent.

4.1.9.2 EXCLUSION CRITERIA:

- Patients with history of intolerance or hypersensitivity to imidazole and allyl amine compounds.
- Use of topical antifungals/topical steroids in treatment area(s) within 30 days of baseline visit.
- All other clinical types of fungal infections like T.capitis, T.barbae etc.,
- Immunocompromised patients.

- Pregnant and lactating mothers.
- Superadded bacterial infections.
- Diabetes mellitus.

4.2 METHODOLOGY

4.2.1 STUDY PROCEDURE:

The study was conducted in patients after obtaining the approval from Institutional Ethics committee. Written informed consent was obtained from all study participants in a prescribed format in regional language after explaining about study purpose and study procedures.

4.2.2 RANDOMISATION:

120 Patients who fulfilled the selection criteria were recruited for the study. After getting informed consent, 60 patients were allotted to each group A and group B respectively. The study participants were randomized by simple randomization method (odd/even number). Complete history, clinical examination and baseline laboratory investigations were taken at the beginning of the study.

GROUP A:

This group consists of 60 patients. All the patients in this group were treated with terbinafine 1% topical cream once daily at bed time for 2 weeks. The patients were advised to apply the cream over the affected skin

approximately 1 inch of the immediate surrounding area once a day for two weeks.

Before starting the therapy fungal infections were confirmed with KOH staining and scrapings were collected from the lesions for mycological culture. Patients were asked to report to the OPD on the first day of every week for a period of two weeks and also on the first day of 4^{th} week. During each visit the clinical signs and symptoms (pruritus, erythema, scaling) were assessed using the 4-point scale and the severity was assessed according to the grading. The patients were assessed by lab investigations. KOH study and mycological culture were done at baseline, 1^{st} week, 2^{nd} week and 4^{th} week. The patients were given drug for 2 weeks and were followed up for a further period of 2 weeks.

GROUP B:

60 patients were recruited in group B. These patients in this group were treated with luliconazole 1% topical cream once daily at bed time for 2 weeks. The cream was applied in the same manner as in group A. Before starting the therapy tinea infections were confirmed with KOH staining and scrapings were collected from the lesions for mycological culture. Patients were asked to report to the OPD on the first day of every week for a period of two weeks and also on the first day of 4^{th} week and improvement was assessed clinically. The lab investigations, KOH study and mycological culture were done as similar to group A. The patients were given drug for 2 weeks and were followed up for a post treatment period of 2 weeks.

4.2.3 ASSESSMENT CRITERIA:

Clinical signs and symptoms (pruritus, erythema, scaling) were assessed using the 4-point scale.(7) as follows

- Pruritus : None = 0, Mild = 1 , Moderate= 2, Severe = 3
- Erythema : None = 0, Mild = 1 , Moderate= 2, Severe = 3
- Scaling : None = 0, Mild = 1 , Moderate= 2, Severe = 3

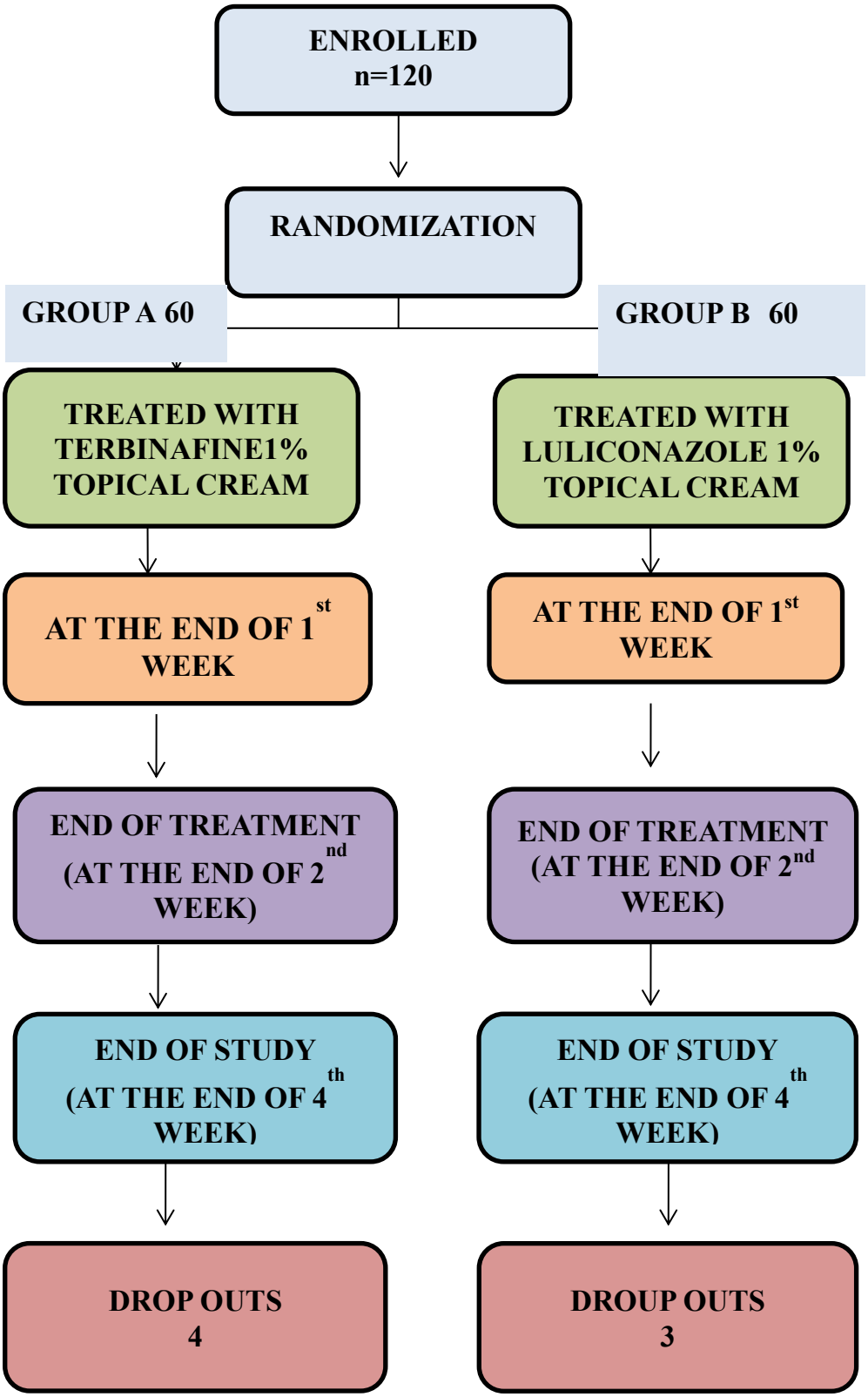
4.2.4 KOH STUDY:

Skin scraping was done after cleaning the lesion thoroughly with 10% alcohol and allowed to dry. Without damaging the skin surface, lesion was scrapped from the periphery, using sterile blunt scalpel(**20**). The collected samples were divided into two portions; the first portion of the sample was used for microscopy using 10% KOH. It was mounted and observed for the presence of fungal hyphae. The second portion of the sample was cultured on Sabourauds dextrose agar and incubated at 25°C for 4-6 weeks for the presence of growth. Mycological identification was done based on macroscopic and microscopic examination. Macroscopic examination included rate of growth, colony morphology and pigment production. Microscopic examination of lactophenol cotton blue mount was done for the presence, shape and arrangement of macro and microconidia.

4.2.5 STATISTICAL ANALYSIS:

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the descriptive data frequency and percentage analysis were used for categorical variables and the mean & standard deviation were used for continuous variables. To find out the significant difference between the bivariate samples in terbinafine (Group A) and luliconazole (Group B) **Mann-Whitney U test** was used. For the multivariate analysis in repeated measures like measuring mean changes within the same group ,the Friedman test followed by the **Wilcoxon Signed rank test** were used. To find the significance in categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 the Fisher's Exact was used. In all the above statistical tools the probability value < .05 is considered as significant level**.** Conclusion regarding the study are discussed in the following chapters.

4.2.6. FLOW CHART SHOWING THE STUDY DESIGN



5. RESULTS

5.1 ANALYSIS OF DEMOGRAPHIC DETAILS:

In each group 60 patients were enrolled and the mean age of patients who were given topical terbinafine cream is 33 and the mean age of group B who were treated with topical luliconazole is 35.

TABLE 5.1 MEAN AGE DISTRIBUTION

GROUPS	N	Mean	Std. Deviation	Independent Samples Test
GROUP A	56	32.29	11.486	P = 0.171
GROUP B	57	35.32	11.878	

, P ≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

This table 5.1 shows mean age for group A and B.

- Since P=0.171 >0.05 there is no statistically significant difference in mean age between the groups.

TABLE 5.2 AGE RANGE AMONG GROUP A AND GROUP B

AGE IN YEARS	GROUP A		GROUP B		Pearson Chi-Square Test
	N	%	N	%	
UPTO 20 YEARS	8	14.3	6	10.5	P = 0.600
21-30 YEARS	18	32.1	19	33.3	
31-40 YEARS	19	33.9	14	24.6	
41 - 50 YEARS	5	8.9	8	14.0	
ABOVE 50 YEARS	6	10.7	10	17.5	
TOTAL	56	57	100	100	

N=Frequency %=Percentage**,** P ≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant.

Table 5.2 displays no statistically significant difference among Group A and Group B regarding distribution of age.

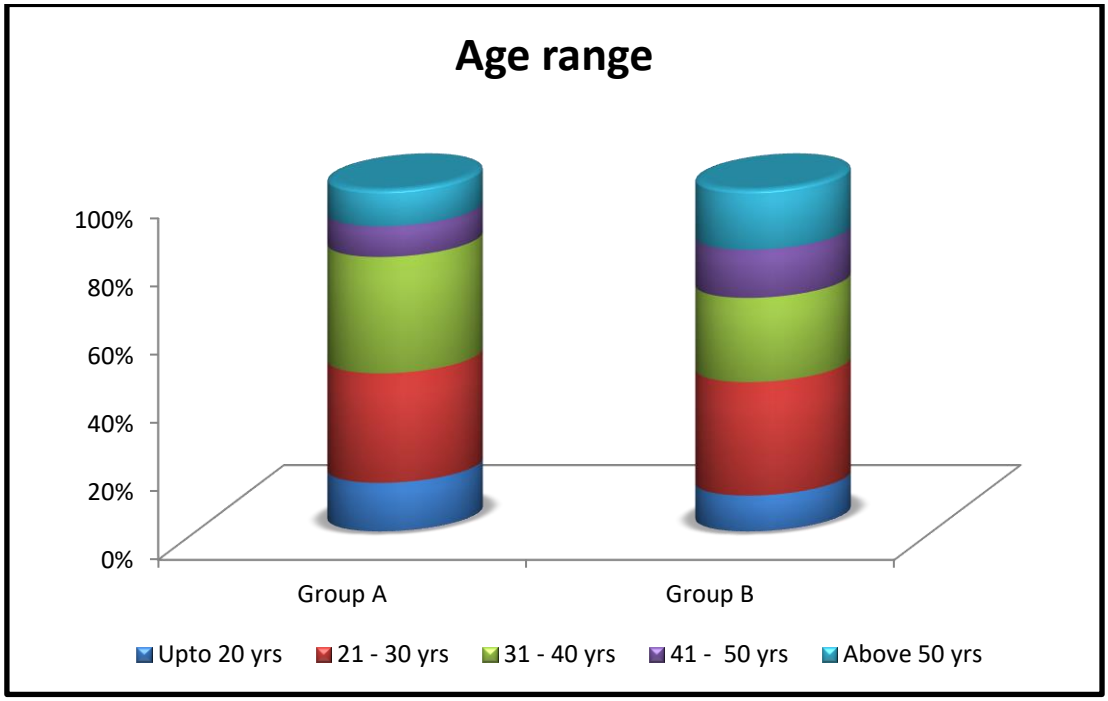


Figure 5.1 Shows age range among Group A and Group B .The patients most commonly affected were in the age range of 20 – 40 years.

TABLE: 5.3 SEX DISTRIBUTION

SEX	GROUP A		GROUP B		PEARSON CHI SQUARE TEST
	N	%	N	%	
MALE	35	62	29	51	P=0.213
FEMALE	21	38	28	49	
TOTAL	56	100%	57	100%	

$P \leq 0.05$ is significant; $P \leq 0.01$ is highly significant; $P \leq 0.001$ is very highly significant

Table 5.3 shows no statistically significant difference among Group A and Group B regarding distribution of gender. Male were more commonly affected than females in both the study groups A and B.

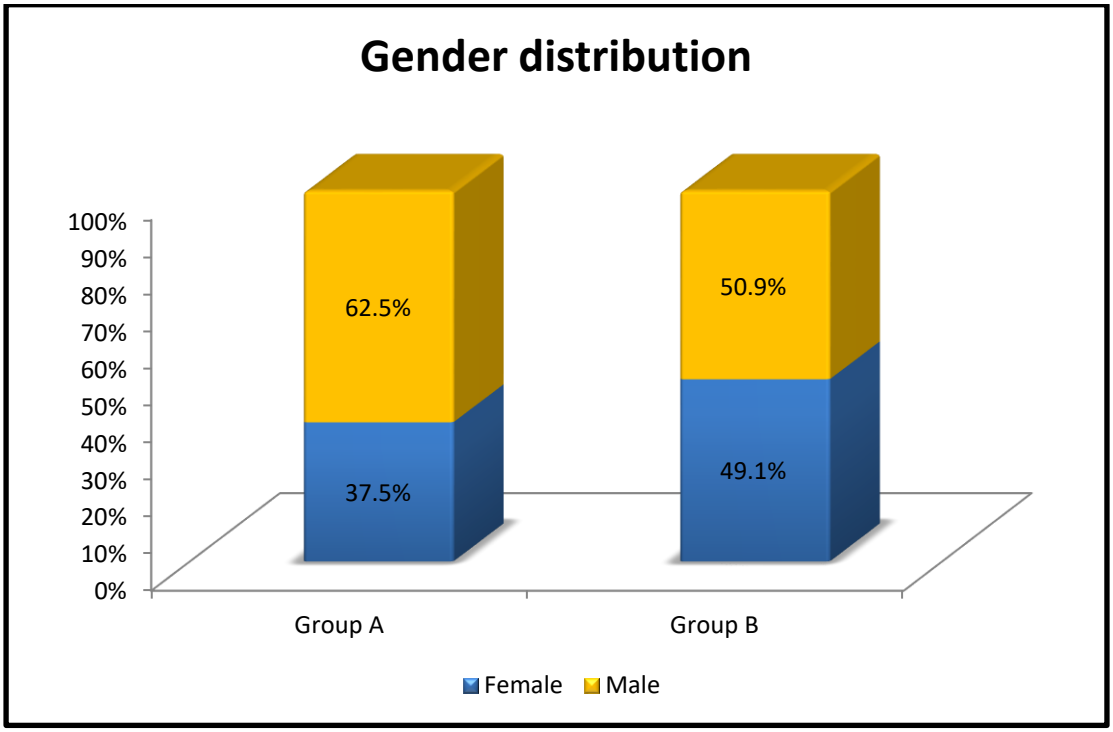


Figure 5.2 shows the graphical representation of sex distribution among Group A & Group B. About 62% and 51% are Males in group A and B respectively. The female constitutes 38% and 49% in group A & group B respectively .There is no significant difference in gender distribution among the groups.

TABLE 5.4 DISTRIBUTION OF DISEASES AMONG PATIENTS IN GROUP A AND GROUP B

DIAGNOSIS	GROUP A		GROUP B		PEARSON CHI SQUARE TEST
	N	%	N	%	
T.CORPORIS	37	66	38	67	0.947
T.CRURIS	19	34	19	33	
TOTAL	56	100	57	100	

N=Number of patients, P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

From the table 5.4 the P value =0.947 (>0.05) shows no statistically significant difference among the Groups regarding distribution of lesion.

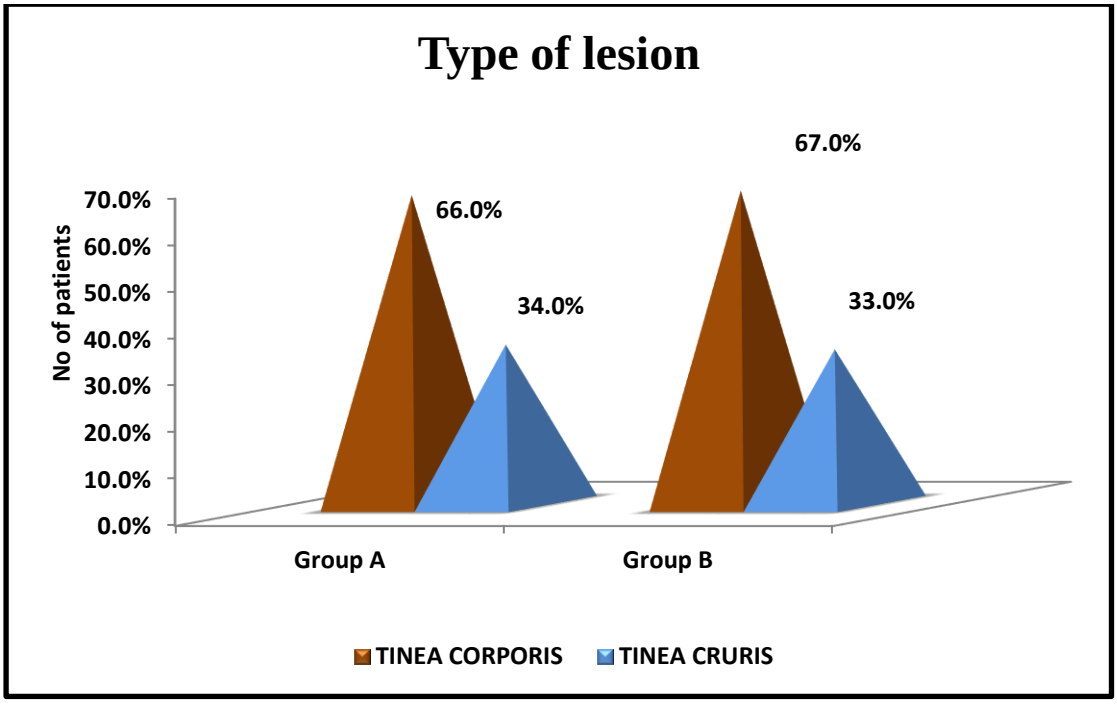


Figure 5.3 shows diagnosis of lesion in group A & group B. The commonest clinical condition observed is tinea corporis which constitutes 66% and 67% in group A and group B respectively followed by tinea cruris which is about 34% and 33% in group A and group B respectively.

TABLE 5.5 DURATION OF THE LESION

DURATION OF THE DISEASE	GROUP A		GROUP B		PEARSON CHI SQUARE TEST
	N	%	N	%	
<2 WEEKS	12	21	10	18	P= 0.576
2 – 3WEEKS	41	73	42	74	
>3 WEEKS	3	5	6	7	
TOTAL	56	100	57	100	

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.5 shows P= 0.576 indicating no statistically significant difference between the two groups.

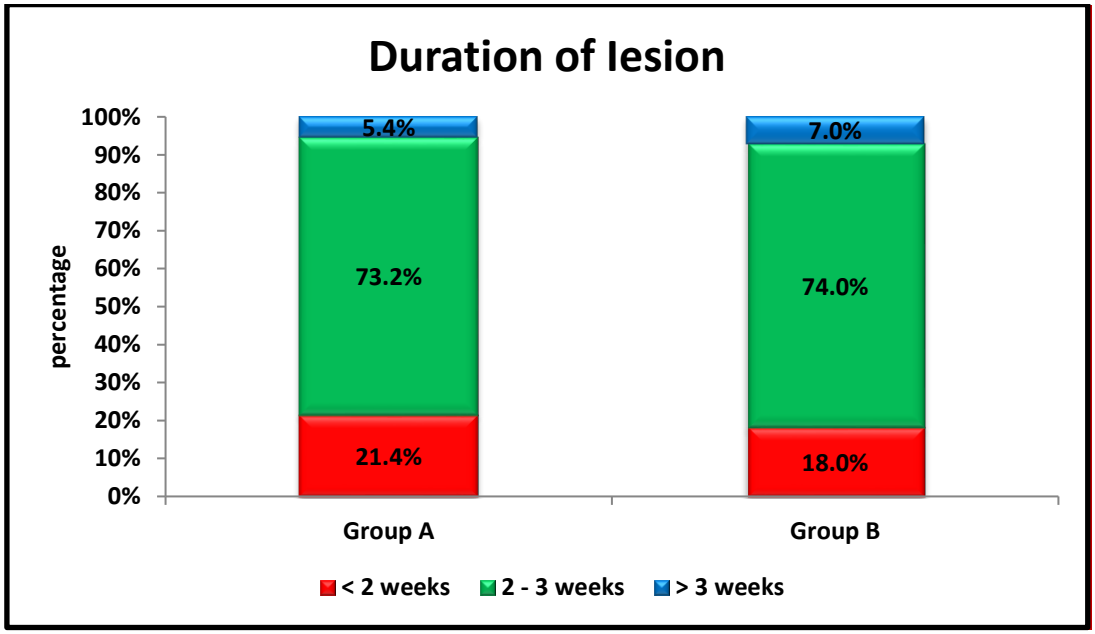


Figure 5.4 shows 21% of the patients in group A and 18% of the patients in group B were having the disease for a period of <2 weeks duration. The 73% and 74% of the patients were presented to the OPD with duration of the illness between 2 – 3 weeks. In the category > 3 weeks, 5% of patients in group A and 7% of patients in group B were presented.

TABLE 5.6 RELATION TO CLIMATE

Relationship to climate	GROUP A		GROUP B		PEARSON CHI SQUARE TEST
	N	%	N	%	
Yes	10	`18	13	23	P = 0.837
No	46	82	44	77	
Total	56	100	57	100	

Table 5.6 shows the relationship of illness to climatic conditions. P value is 0.837.This is not statistically significant.

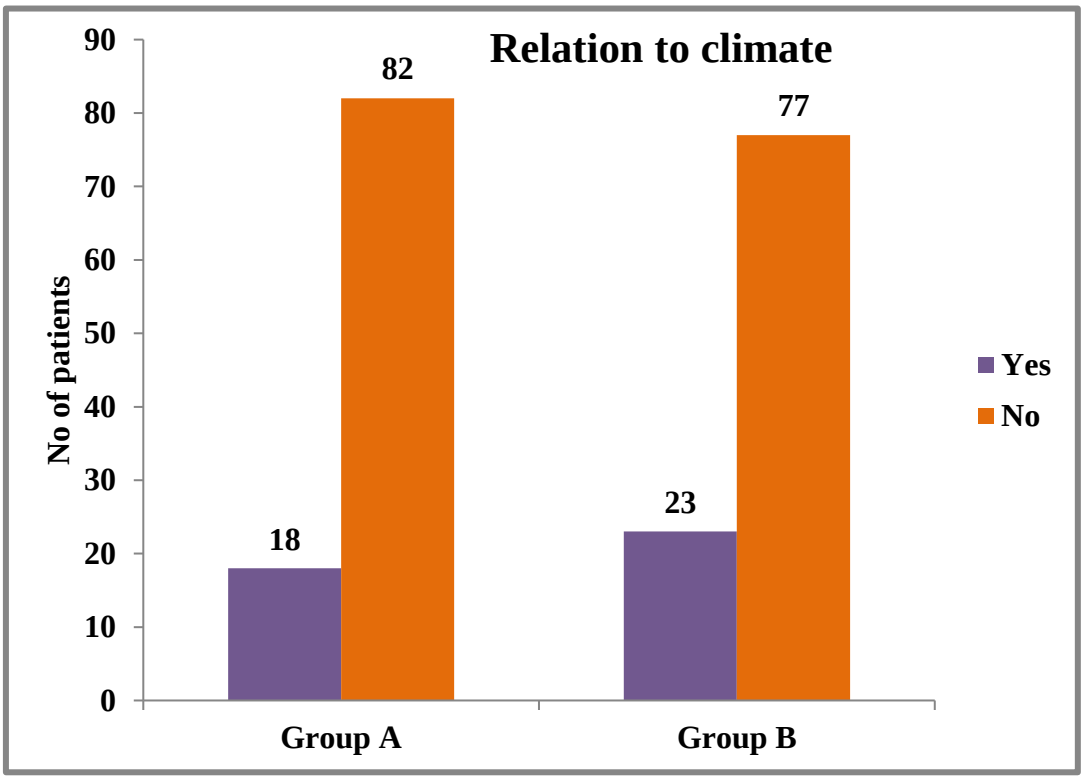


Figure 5.5 shows 18% of patients in group A and 23% of patients in group B having hot humid climatic correlation with occurrence of the disease.

TABLE 5.7 HISTORY OF SIMILAR INFECTION IN THE FAMILY AMONG PATIENTS

CONTACT HISTORY	GROUP A		GROUP B		Pearson chi square test
	N	%	N	%	
YES	8	14	8	14	P=0.970
NO	48	86	49	86	
TOTAL	56	100	57	100	

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.7 represents P>0.05 there is no statistically significant difference.

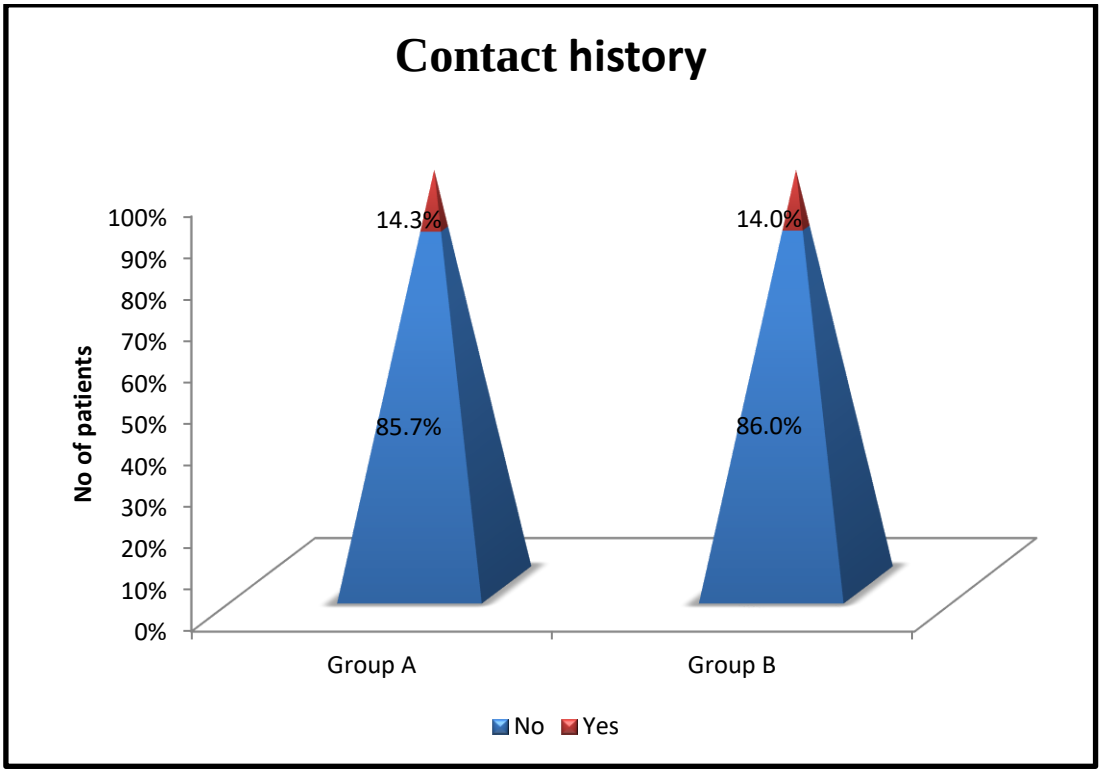


Figure 5.6 shows history of members having similar fungal infections. 14% of patients in each group had history of family members suffering from the similar infection. For analyzing demographic details, Pearson chi-square test is used and percentage bar diagram has also been presented.

5.2 ANALYSIS OF DRUG EFFECTS IN THE TRIAL GROUPS

Wilcoxon signed ranks test is used for analyzing the changes over time and its significance. In this test mean rank is used for analysis. **Mean rank** implies reduction in the pruritis mean score from baseline.

Mann-Whitney Test is uses the **Z** value for comparison between group A and group B and also to find out the statistical difference between the groups.

5.2.1. PRURITUS SCORE-Wilcoxon Signed Ranks Test

TABLE 5.8 CHANGES IN PRURITUS MEAN SCORE FROM BASELINE IN GROUP A

GROUP A	N	Mean	Standard deviation	Mean Rank	Z	Wilcoxon Signed Ranks Test
Base line	56	2.04	0.538			
Base line- 1st week	56	0.91	0.769	**21**	**-5.741**	P = 0.0005
Base line- 2nd week	56	0.32	0.471	28.50	-6.649	P = 0.0005
Base line- 4th week	56	0.18	0.386	28.50	-6.712	P = 0.0005

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.8 depicts the reduction in pruritus mean score from baseline at the end of 1st week, 2nd week and 4th week in group A.

- A significant decrease was seen in all the three visits (P≤ 0.05) within group A.
- The reduction was higher from the baseline to 1st week (i.e. Mean rank = 21, Z = -5.741).

TABLE 5.9. REDUCTION OF PRURITUS MEAN SCORE FROM BASELINE IN GROUP B

GROUP B	N	Mean	Standard deviation	Mean Rank	z	Wilcoxon Signed Ranks Test Asymp. Sig. (2-tailed)
Base line	57	1.95	0.610			
Base line- 1st week	57	0.60	0.651	**23.5**	**-6.069**	P = 0.0005
Base line- 2nd week	57	0.16	0.368	28	-6.620	P = 0.0005
Base line- 4th week	57	0.07	0.258	28.5	-6.695	P = 0.0005

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.9 demonstrates the reduction in pruritus mean score from baseline at the end of 1st week, 2nd week and 4th week in group B.

- A statistically significant decrease was seen in all the three visits (P≤ 0.05).
- The fall in pruritus score is higher in the time interval from baseline to 1st week (i.e. Mean rank = 23.5, Z = -6.069).

TABLE 5.10 COMPARISON OF REDUCTION OF MEAN PRURITUS SCORING BETWEEN GROUP A AND GROUP B

PRURITUS	GROUPS	N	Mean	Std. Deviation	Mean rank	Z	Mann-Whitney Test
BASELINE	Group A	56	2.04	0.538	59.12	-0.821	0.412
	Group B	57	1.95	0.610	54.92		
1ST WEEK	Group A	56	0.91	0.769	59.12	-2.197	**0.028**
	Group B	57	0.60	0.651	54.92		
2ND WEEK	Group A	56	0.32	0.471	61.66	-2.029	0.042
	Group B	57	0.16	0.368	52.42		
4TH WEEK	Group A	56	0.18	0.386	60.09	-1.741	0.082
	Group B	57	0.07	0.258	53.96		

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.10 showing the changes in pruritus mean score between group A & group B are compared for all the three visits (1st , 2nd and 4th week).

- A statistically significant difference is observed in 1st and 2nd week.
- This difference is noticeable at the end of 1st week (P=0.028).

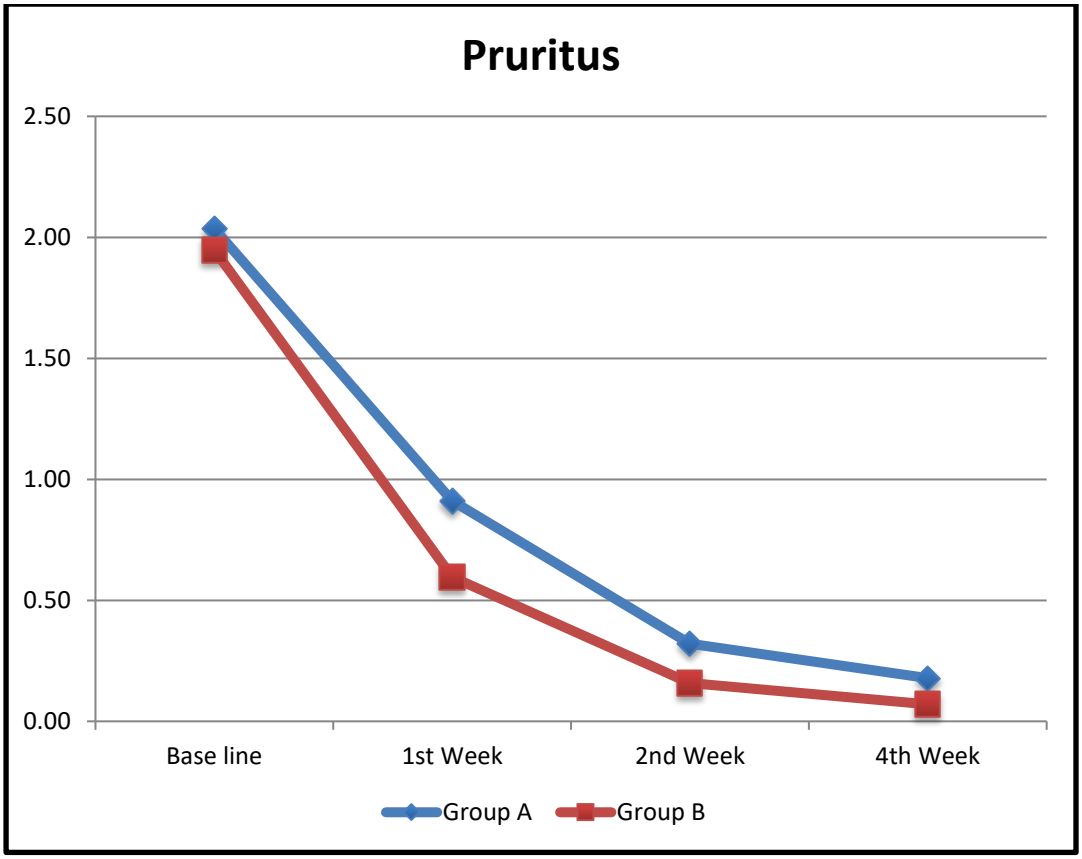


Figure 5.7 shows graphical representation of changes in mean pruritus score during each visit between group A & group B.

- The decline in mean pruritus score is higher at the end of 1st week when compared to 2nd week and 4th week in both group A and group B.
- The reduction in the score is higher in group B when compared to group A.

5.2.2 ERYTHEMA SCORE

TABLE 5.11 CHANGES IN ERYTHEMA MEAN SCORE FROM BASELINE TO EACH VISIT IN GROUP A

GROUP A	N	Mean	Standard deviation	Mean Rank	z	Wilcoxon Signed Ranks Test Asymp. Sig. (2-tailed)
Base Line	56	1.98	0.646			
Base line- 1st week	56	0.82	0.636	**25.5**	**-6.468**	P = 0.0005
Base line- 2nd week	56	0.30	0.464	28.5	-6.708	P = 0.0005
Base line- 4th week	56	0.27	0.447	28.5	-6.702	P = 0.0005

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.11 depicts the reduction in erythema mean score from baseline at the end of 1st week, 2nd week and 4th week.

- A highly significant decrease was seen in all the three visits (P≤ 0.05) within group A.
- Higher decrease in score was observed in the time interval from baseline to 1st week (i.e. Mean rank = 25.5, Z = -6.468).

TABLE 5.12 CHANGES IN ERYTHEMA MEAN SCORES FROM BASELINE TO EACH VISIT IN GROUP B

GROUP B	N	Mean	Standard deviation	Mean Rank	Z	Wilcoxon Signed Ranks Test Asymp. Sig. (2-tailed)
Base line	57	1.89	0.795			
Base line-1st week	57	0.56	0.567	**24**	**-6.106**	P = 0.0005
Base line-2nd week	57	0.14	0.350	27.5	-6.534	P = 0.0005
Base line-4th week	57	0.11	0.310	27.5	-6.531	P = 0.0005

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.12 depicts the reduction in erythema mean score from baseline at the end of 1st week, 2nd week and 4th week in group B.

- A highly significant decrease was observed in all the three visits

(P≤ 0.05) in group B.

- Higher decrease in score was observed in the time interval from baseline to 1st week (i.e. Mean rank = 24, Z = -6.106).

TABLE 5.13 COMPARISON OF REDUCTION OF MEAN ERYTHEMA SCORING BETWEEN GROUP A AND GROUP B

ERTHEYMA	GROUPS	N	Mean	Std. Deviation	Mean rank	Z	Mann-Whitney Test
BASELINE	group A	56	1.98	0.646	58.13	-0.402	0.687
	Group B	57	1.98	0.646	55.89		
1ST WEEK	Group A	56	0.82	0.636	63.00	-2.197	**0.028**
	Group B	57	0.56	0.567	**51.11**		
2ND WEEK	Group A	56	0.30	0.464	61.65	-2.081	0.037
	Group B	57	0.14	0.350	52.43		
4TH WEEK	Group A	56	0.27	0.447	61.63	-2.212	0.027
	Group B	57	0.11	0.310	52.45		

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.13 showing the changes in erythema mean score between group A & group B are compared for all the three visits (1st, 2nd and 4th week).

- A statistically significant difference was noted in all the three visits (P≤ 0.05).The significance was more marked at the end of 1st week.

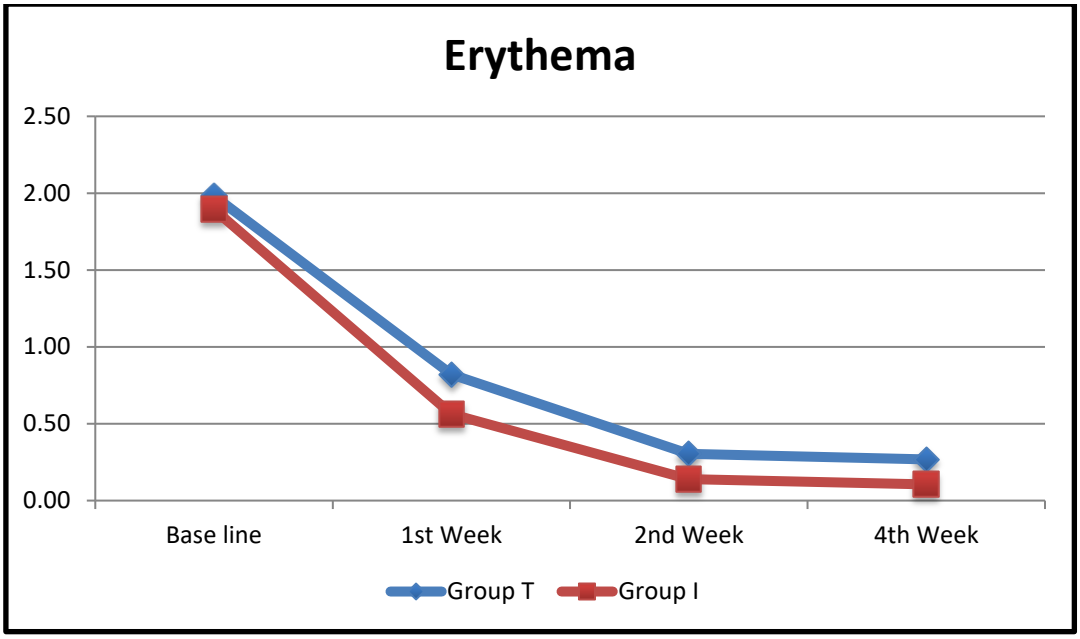


Figure 5.8 shows graphical representation of mean erythema scores during each visit.

- Marked reduction in erythema mean score is seen at the end of 1st week in both group A and group B.
- The decrease in the erythema mean score was higher in the group B

TABLE 5.14 CHANGES IN SCALING MEAN SCORES FROM BASELINE TO EACH VISIT IN GROUP A

GROUP A	N	Mean	Standard deviation	Mean Rank	Z	Wilcoxon Signed Ranks Test Asymp. Sig. (2-tailed)
Base line	56	1.71	0.624			
Base line- 1st week	56	0.61	0.623	**24.5**	**-6.329**	P = 0.0005
Base line- 2nd week	56	0.18	0.386	28	-6.617	P = 0.0005
Base line- 4th week	56	0.14	0.353	28	-6.608	P = 0.0005

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant.

The table 5.14 represents the reduction in scaling mean score from baseline to all the three visits.

- A highly significant decrease was seen in all the three visits (P≤ 0.05) within group A.
- Higher decline in score was observed in the time interval from baseline to 1st week (i.e. Mean rank = 24.5, Z = -6.329).

TABLE 5.15 CHANGES IN SCALING MEAN SCORES FROM BASELINE TO EACH VISIT IN GROUP B

GROUP B	N	Mean	Standard deviation	Mean Rank	Z	Wilcoxon Signed Ranks Test Asymp. Sig. (2-tailed)
Base line	56	1.72	0.726			
Base line- 1st week	57	0.42	0.565	**24**	**-6.117**	P = 0.0005
Base line- 2nd week	57	0.19	0.398	27	-6.475	P = 0.0005
Base line- 4th week	57	0.12	0.331	27	-6.479	P = 0.0005

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.15 represents the reduction in scaling mean score from baseline to all the three visits.

- A highly significant decrease was seen in all the three visits (P≤ 0.05) within group B.
- Decline in score was observed in the time interval from baseline to 1st week (i.e. Mean rank = 24, Z = -6.117).

TABLE 5.16 COMPARISON OF REDUCTION OF MEAN SCALING SCORE BETWEEN GROUP A AND GROUP B

SCALING	GROUPS	N	Mean	Std. Deviation	Mean rank	Z	Mann-Whitney Test
BASELINE	Group A	56	1.71	.624	56.20	-0.289	0.772
	Group B	57	1.72	.726	57.79		
1ST WEEK	Group A	56	.61	.623	61.52	-1.650	**0.028**
	Group B	57	.42	.565	**52.56**		
2ND WEEK	Group A	56	.18	.386	56.59	-0.196	0.845
	Group B	57	.19	.398	57.40		
4TH WEEK	Group A	56	.14	.353	57.57	-0.196	0.755
	Group B	57	.12	.331	56.44		

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

In table 5.16 showing the changes in scaling mean score between group A & group B are compared for all the three visits (1st , 2nd and 4th week).

- A statistically significant difference is observed in 1st week (Mean =52.56, P=0.028).
- There was no statistical difference noticed at the end of 2nd and 4th week.

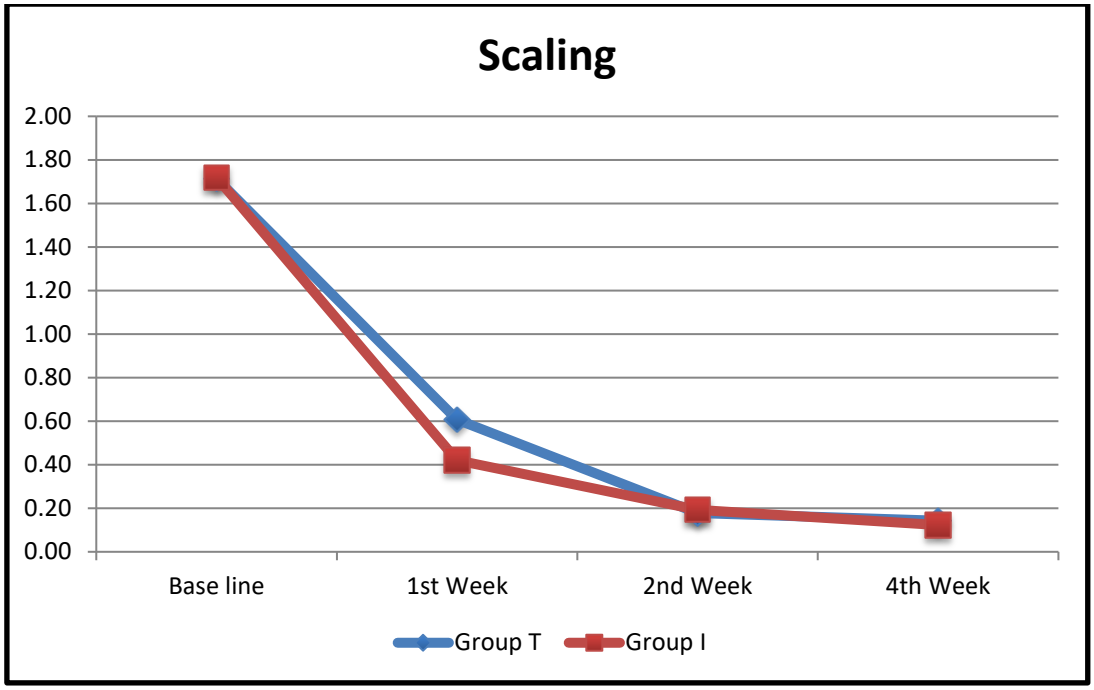


Figure 5.9 shows a graphical representation of changes in scaling score during each visits.

- There is a reduction in mean scaling scores from baseline, at the end of 1st week, 2nd week and 4th week.

TABLE 5.17 COMPARISON OF PERCENTAGE REDUCTION IN MEAN COMPOSITE SCORE BETWEEN GROUP A AND GROUP B

VISITS	GROUP A			GROUP B		
	Mean composite score	Reduction in mean composite score from base line	%	Mean	Reduction in mean composite score from baseline	%
Baseline	5.73		100	5.56		100
1st week	2.34	3.39	**59**	1.58	3.98	**72**
2nd week	0.80	4.93	**86**	0.49	5.07	**91**
4th week	0.61	5.12	89	0.30	5.26	93

Table 5.17 shows percentage reduction in mean composite score from baseline to 1st week, 2nd week and 4th week. There is 59% and 72% reduction in the mean composite score in group A and group B respectively at the end of 1st week. At the end of 2nd week the reduction is 86% in group A and 91% in group B. Effective response is seen at the end of 1st week in group B than group A.

5.3 COMPARISON OF LAB INVESTIGATIONS OF GROUP A WITH GROUP B

5.3.1 KOH STUDY:

Before starting therapy all the patients are examined for the presence of fungal filaments under microscope and they are positive in both the groups as represented in the table.

TABLE 5.18 COMPARISON OF KOH RESULTS BETWEEN GROUP A AND GROUP B

VISITS	GROUP A				GROUP B				PEARSON CHI-SQUARE
	KOH POSITIVE		KOH NEGATIVE		KOH POSITIVE		KOH NEGATIVE		
	N	%	N	%	N	%	N	%	
BASE LINE	56	100	-	-	57	100	-	-	
1ST WEEK	22	39	34	61	8	14	49	86	**P= 0.03**
2ND WEEK	3	5	53	95	2	4	55	96	P=0.364
4TH WEEK	3	5	53	95	0	0	57	100	P=0.118

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.18 shows comparison of KOH results between group A and group B, One week after therapy fungal filaments were absent in 61% of group A patients and 86% in group B. There is a statistically significant difference seen at the end of first week with a P value < 0.05 between two groups. There is no statistical significant difference seen between two groups at the end of 2nd and 4th week.

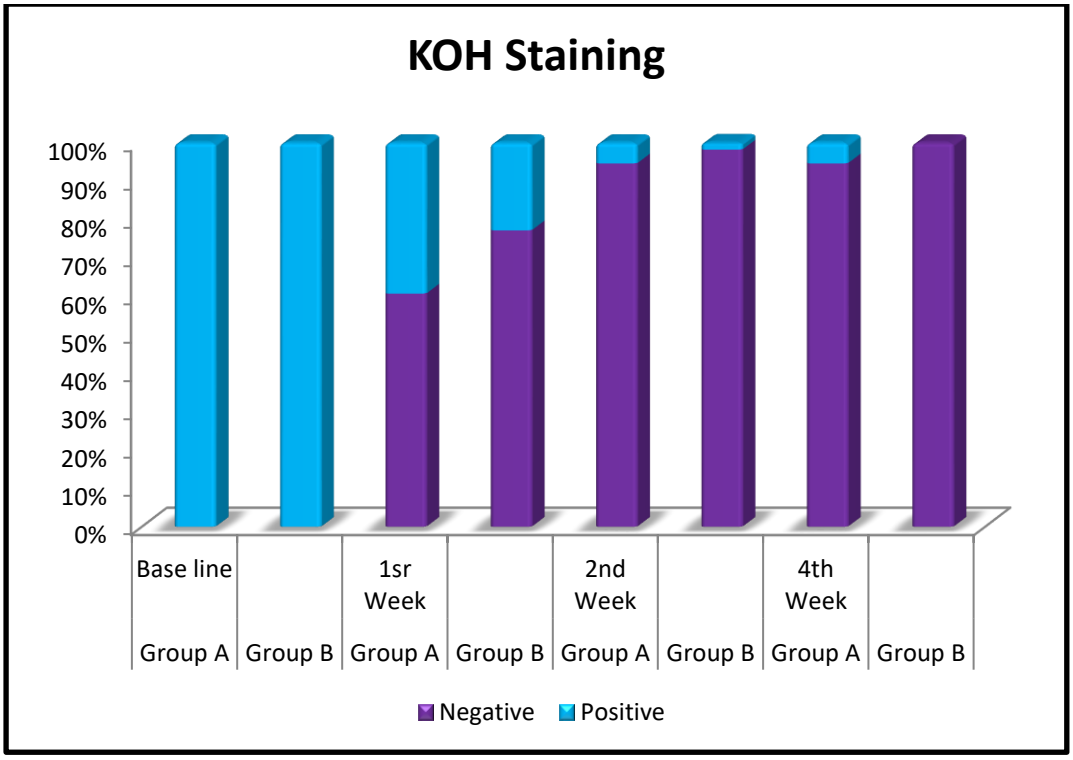


Figure 5.11 shows graphical representation of KOH results between group A and group B.

5.3.2 MYCOLOGICAL CULTURE:

Mycological culture was done and positive in all the patients before starting therapy.

TABLE 5.19 COMPARISON OF SPECIES IDENTIFIED AMONG GROUP A AND GROUP B AT BASELINE

SPECIES	Group A		Group B		Pearson chi square test
	N	%	N	%	
E.floccosum	3	5.4	4	7	P = 0.683
T.mentagrophytes	16	28.6	13	22.8	
T.rubrum	37	66.1	40	70.2	
Total	56	100	57	100	

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

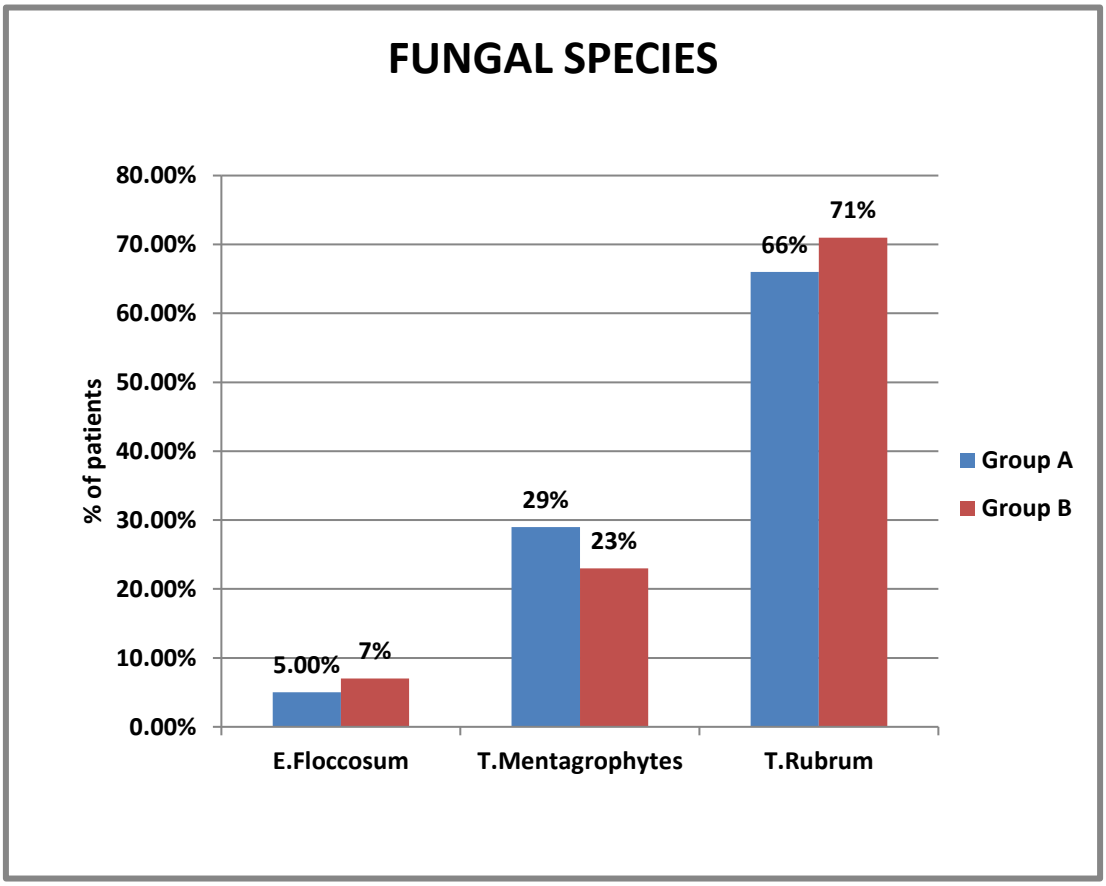


Figure 5.12 shows 71% and 66% of patients in group A and group B harbouring *Trichophyton rubrum* species were identified in the fungal culture which constitutes the predominant isolate in the study. This is followed by *T. mentagrophytes* and then *E.flocossum*

TABLE 5.20 FUNGAL CULTURE RESULT

VISITS	GROUP A				GROUP B				PEARSON CHI SQUARE TEST
	CULTURE POSITIVE		CULTURE NEGATIVE		CULTURE POSITIVE		CULTURE NEGATIVE		
	N	%	N	%	N	%	N	%	
BASE LINE	56	100	-	-	57	100	-	-	
1ST WEEK	18	33	38	67	7	12	50	88	**P = 0.03**
2ND WEEK	3	5	53	95	2	4	55	96	P = 0.495
4TH WEEK	0	0	56	100	0	0	57	100	P = 0.208

P≤ 0.05 is significant; P ≤ 0.01 is highly significant; P ≤ 0.001 is very highly significant

Table 5.20 shows results of fungal culture done at baseline, at the end of 1st week, 2nd week and 4th week.

- At the end of 1st week, p = 0.03, which is statistically significant in between the study groups.

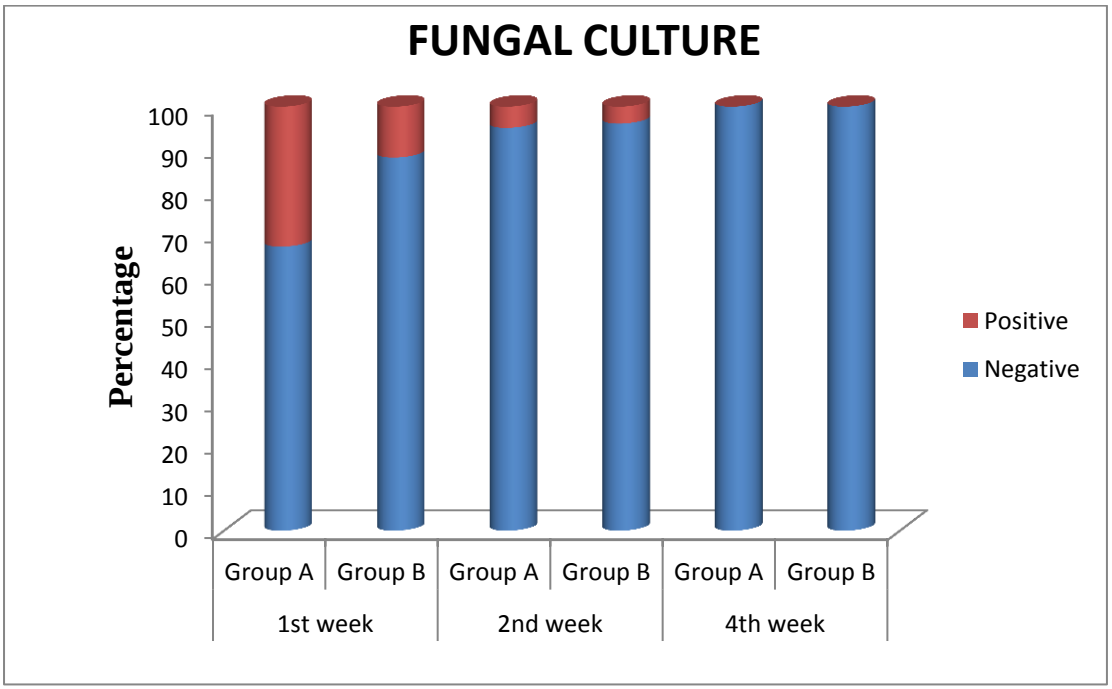


Figure 5.13 shows a graphical representation of fungal culture result during each visit in comparison between group A and group B.

- At the end 1st week the culture was negative in 67% and 88% of patients in group A and group B respectively.

TABLE 5.21 COMPARISON OF ADVERSE EVENTS

Group	Adverse events		Total	Chi-square test
	Present	Absent		
Group A	3	53	56	P = 0.6
Group B	2	56	58	

*P≤ 0.05=Significant; **P≤0.0= highly significant, ***P≤0.001=very highly significant.

- Three patients in group A experienced burning sensation (2),and mild contact dermatitis (1) and two patients in group B reported contact dermatitis but the occurrence of adverse effects did not require interruption of therapy .

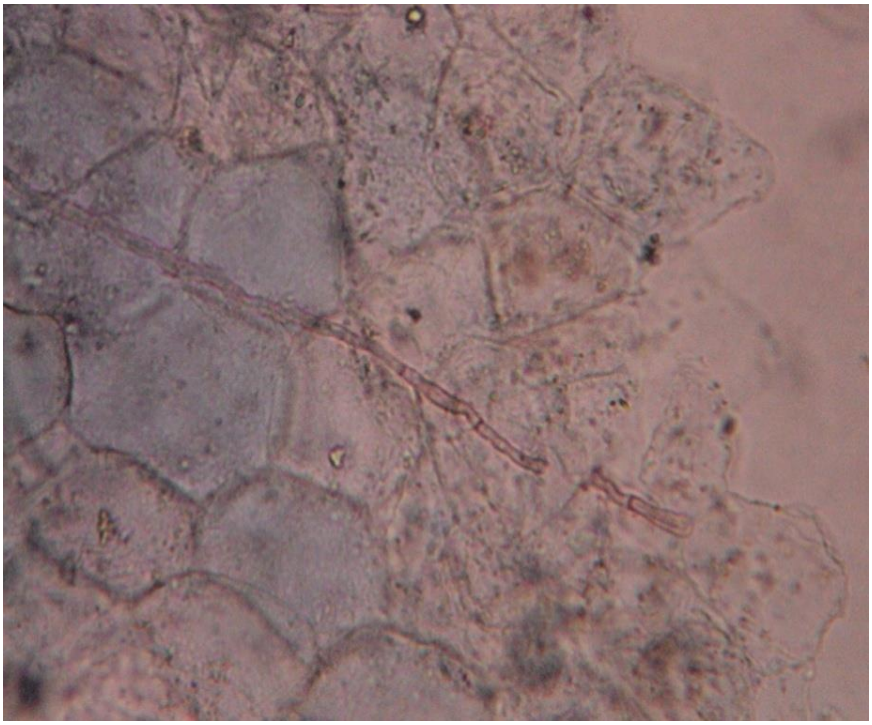


Figure 5.14 KOH Mount showing fungal elements

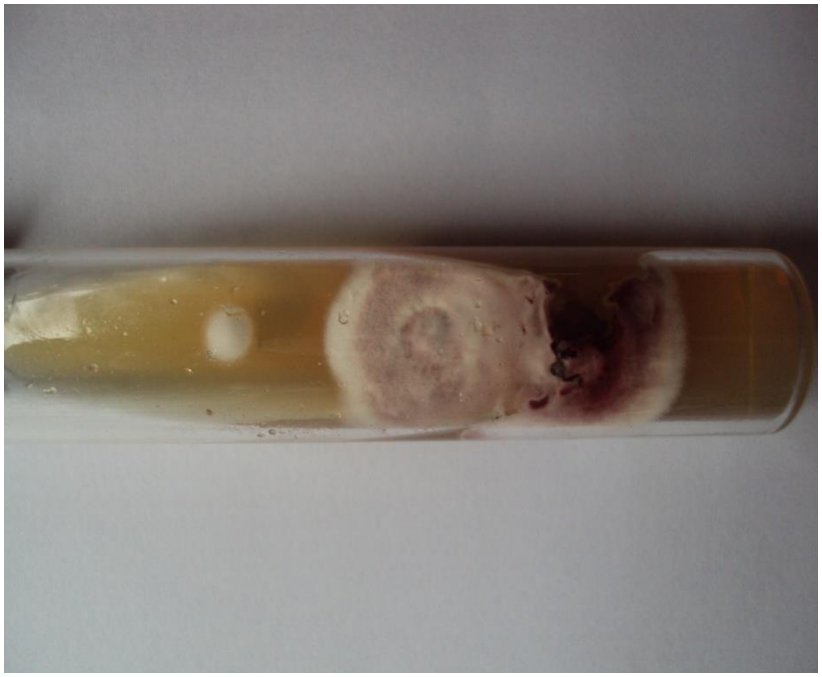


Figure 5.15 *Trichophyton rubrum* growing on SDA medium

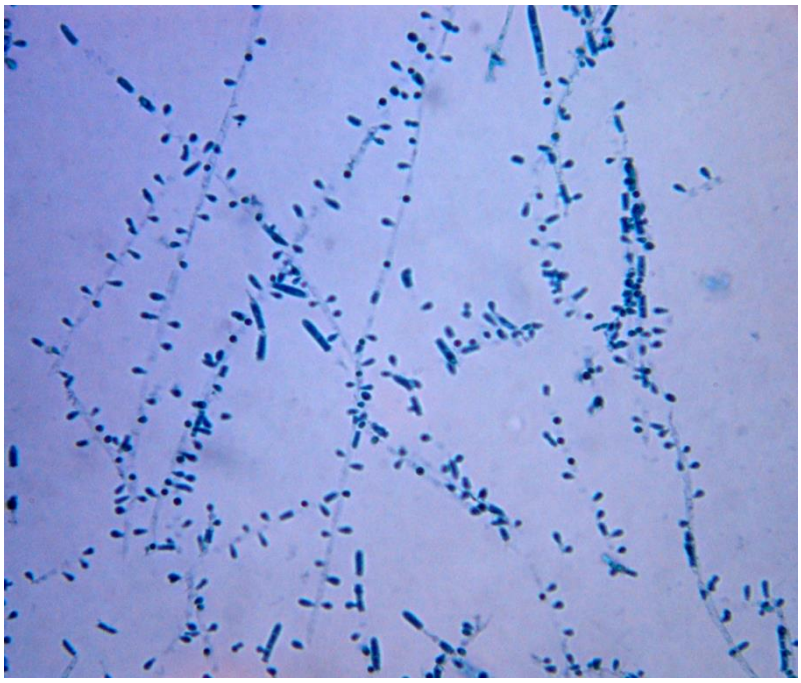


Figure 5.16 *Trichophyton rubrum* in LPCB staining

Figure 5.17 *Trichophyton mentagrophytes* on SDA medium

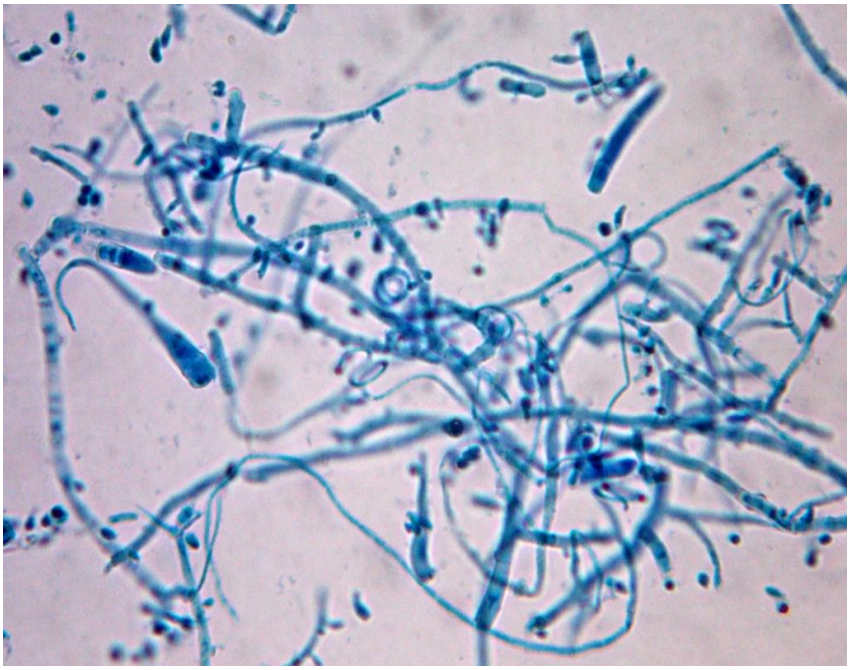


Figure 5.18 *Trichophyton mentagrophytes* in LPCB staining

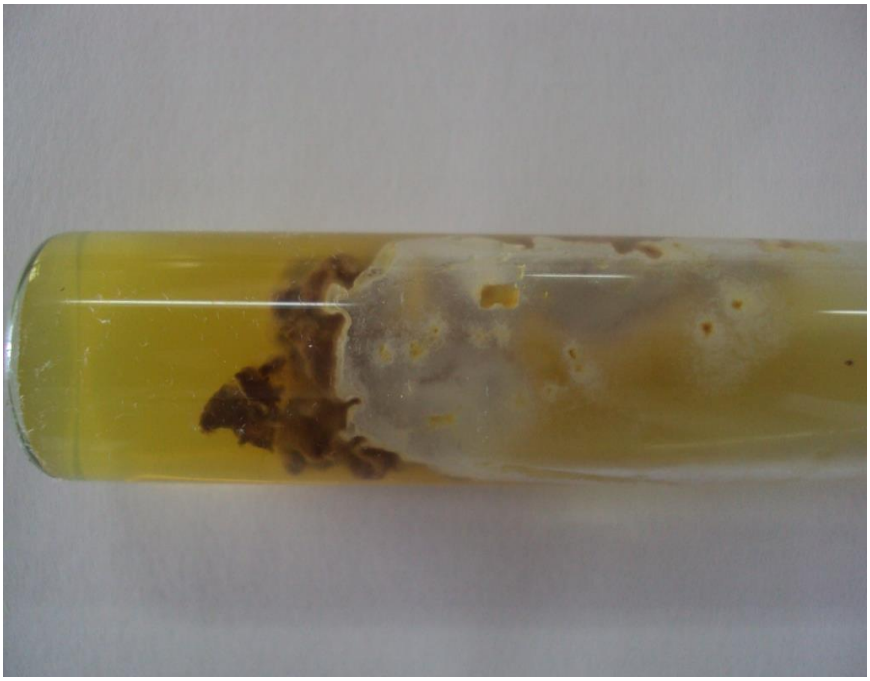


Figure 5.19 *Epidermophyton floccosum* on SDA medium

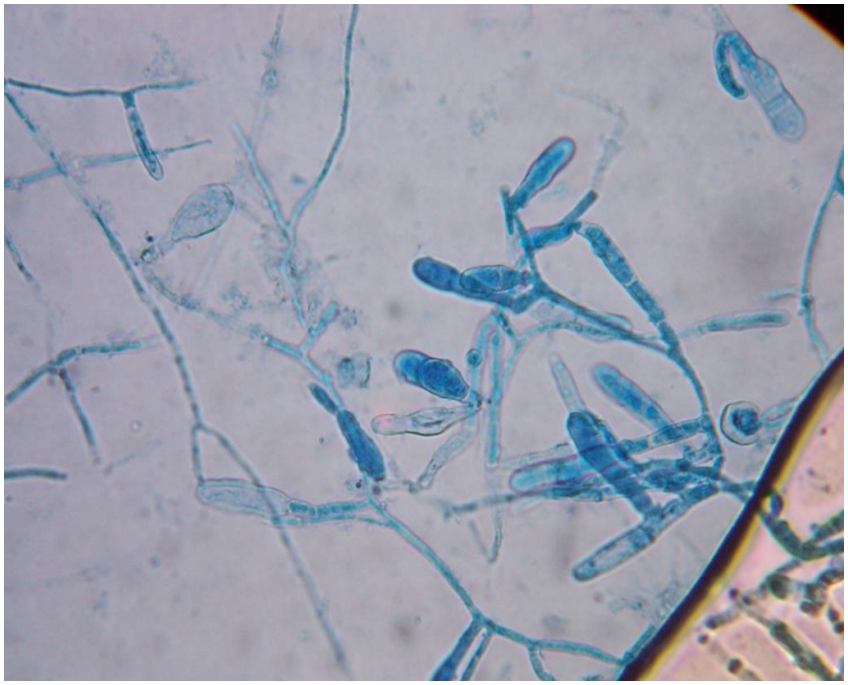


Figure 5.20 *Epidermophyton floccosum* in LPCB staining

Figure 5.21 (a) Clinical condition of tinea cruris lesion before treatment with topical terbinafine.

Figure 5.22 (b) Clinical condition of tinea cruris lesion before treatment with topical terbinafine.

Figure 5.23 (a) Clinical condition of tinea corporis lesion before treatment with topical terbinafine

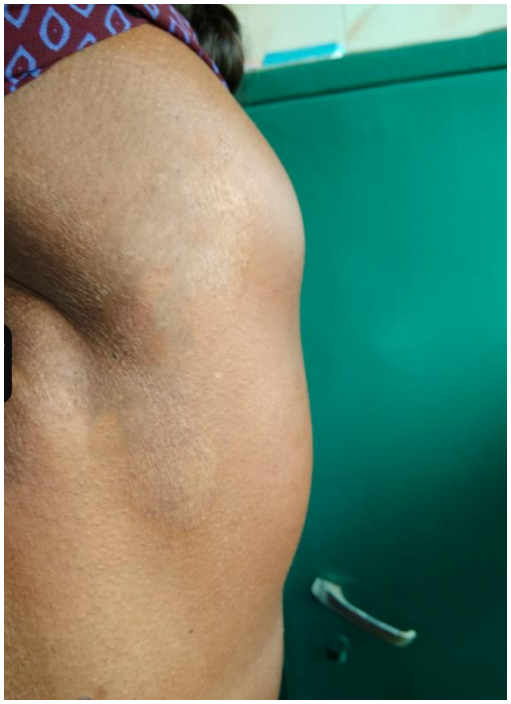


Figure 5.24 (b) Improvement in tinea corporis lesion 2 weeks after treatment with topical terbinafine.

Figure 5.25 (a) Clinical condition of tinea cruris lesion before treatment with topical LLCZ.

Figure 5.26 (b) Improvement in tinea cruris lesion 2 weeks after treatment with LLCZ

Figure 5.27 (a) Clinical condition of tinea corporis before treatment with topical Luliconazole.

Figure 5.28 (b) Improvement in tinea corporis lesion 2 weeks after treatment with topical luliconazole.

6. DISCUSSION

The study was conducted for comparing the efficacy and tolerability of terbinafine 1% cream and luliconazole 1% cream in tinea corporis and tinea cruris patients. Patients diagnosed with tinea corporis and tinea cruris in the OPD of dermatology in Chengalpattu medical college were randomized into group A and group B. Out of 120 patients 114 patients completed the study, 3 patients and 2 patients in group A and Group B respectively were withdrawn from the study due to non-willingness to continue the study. 56 patients in group A and 57 patients in group B completed the study.

The prevalence of tinea corporis and cruris is more common in the age range of 21 to 40 years and this sex predominance is attributed to increased physical activity and increased sweating in the young active group of people. The mean age is 33 and 35 years in terbinafine and luliconazole group which is similar with Sudha *et al*., study. Male were more commonly affected in both the groups because perspiration is more common in male than female. Excessive perspiration removes protective anti-fungal fatty acids in the skin predisposing to dermatophyte infection. The ratio of male to female is 1.3: 1

The most common clinical infection observed was Tinea corporis followed by Tinea cruris .There is no significant difference among the patients of both groups while comparing climatic condition and family history of contact with similar lesion.

ANALYSIS OF DRUG EFFECTS IN GROUP A AND GROUP B

The statistical results were analyzed with respect to group and time.

- **Group effect** was described as the comparison of response to treatment between topical LLCZ 1% cream (Group A) with topical terbinafine 1% cream (Group B). The significant differences in p value between two groups in favour of any of the groups were derived using Mann-**Whitney U Test** which compared efficacy between group A and group B
- **Time effect** was observed as significant reduction in clinical signs and symptoms scores of pruritus, erythema and scaling from baseline with respect to 1st week (T1), 2nd week (T2) and 4th week (T3) in each group. **Wilcoxon signed ranks test** was used for analyzing the changes over time and its significance between the time intervals. In this test **mean rank** was used for analysis. **Mean rank** implies reduction in the symptom mean score from baseline.

TIME EFFECT AT THE END OF 1ST WEEK (T1) IN TERBINAFINE GROUP:

While analyzing the time effect in terbinafine group the results revealed a reduction in **mean pruritus score** from baseline to 1st week (T1). A statistically significant decrease was seen in all the three visits ($P \leq 0.05$). The mean rank for pruritus were T1= 21, T2 = 28.50 and T3 = 28.50. This shows a significant reduction with $P \leq 0.005$ was noted at the end of 1st week (T1).

Hence lowest value mean score value was observed in the time interval between baseline to 1st week. (i.e. Mean rank = 21, Z = -5.741) when compared with other time intervals and it was represented in the table 5.8.

By analyzing the results of **erythema mean score** at the end of 1st week, the decline in the mean score from base line to all subsequent visits were as follows: T1 = 25.5, T2 = 28.5, T3 = 28.5 from these values it is inferred that significant reduction was seen in the time interval from baseline to 1st week (T1= 25.5 [i.e. Mean rank), Z = -6.468). Also a highly significant statistical difference was seen in all the three visits ($P \leq 0.05$).

While analyzing the **scaling mean score** in the terbinafine group the mean rank changes in each visit are as follows: T1 = 24.5, T2=28, T3= 28. A statistically difference is noted with a $P \leq 0.05$ in all the three visits. Changes in mean score was high at baseline to 1st week the Mean rank = 23.5 & Z= -6.069. After determining the analysis results of all the signs and symptoms at the end of first week, the reduction in the mean scores indicates the therapeutic responses with terbinafine treatment.

TIME EFFECT AT THE END OF 1ST WEEK (T1) IN LULICONAZOLE GROUP:

While analyzing the time effect in LLCZ group the results revealed a reduction in **mean pruritus score** from baseline to 1st week (T1). A statistically significant decrease was seen in all the three visits

(P≤ 0.05). The mean rank for pruritus were T1= 23.5, T2 = 28 and T3 = 28.50. This shows a significant reduction with P≤ 0.005 was noted at the end of 1st week (T1).

Hence lowest value mean score value was observed in the time interval between baseline to 1st week. (i.e. Mean rank = 23.5, Z = 6.069) when compared with other time intervals and it was represented in the table 5.9.

By analyzing the results of **erythema mean score** at the end of 1st week, the decline in the mean score from base line to all subsequent visits were as follows: T1 = 24, T2 = 27.5, T3= 27.5 from these values it is inferred that significant reduction was seen in the time interval from baseline to 1st week (T1= 24 [i.e. Mean rank), Z = -6.106). Also a highly significant statistical difference was seen in all the three visits (P≤ 0.05).

While analyzing the **scaling mean score** in the terbinafine group the mean rank changes in each visit are as follows: T1 = 24, T2=27, T3= 27. A statistically difference is noted with a P≤ 0.05 in all the three visits. Changes in mean score was high at baseline to 1st week the Mean rank =24 & Z= 6.117. After determining the analysis results of all the signs and symptoms at the end of first week, the reduction in the mean scores indicates the therapeutic responses with terbinafine treatment.

GROUP EFFECTS were analyzed using Mann-Whitney U Test with the results derived from the reductions in pruritus, erythema, and scaling mean scores between TBF 1% cream and the LLCZ group at the end of 1st week.

The pruritis mean rank of TBF and LLCZ groups were 59.12 & 54.92 respectively and P = 0.412. A Statistically significant reduction was noted in the 1 % LLCZ group. Hence the effectiveness of 1 % LLCZ is evident from these analysis.

The erythema mean rank of TBF and LLCZ groups were 63.00 & 51.11 respectively and P = 0.028. A Statistically significant reduction was noted in the 1% LLCZ group. Hence the effectiveness of 1 % LLCZ is higher than 1% TBF reducing the erythema.

The scaling mean rank of TBF and LLCZ groups were 61.52 & 52.56 respectively and P = 0.028. A Statistically significant difference was noted in the 1% LLCZ group. Hence 1% LLCZ was highly efficacious in reducing the scaling symptom from these analysis.

ANALYSIS OF RESULTS AT END OF SECOND WEEK

The reduction in the mean pruritis score (Mean rank = 28), mean erythema score (Mean rank =27.5), mean scaling score (Mean rank =27) showed a statistically significant difference with a P value (≤0.05) was obtained in the terbinafine as well as in the luliconazole group. But the mean rank was lower than that obtained at the end of 1st week. Eventhough both the drugs were effective in providing therapeutic response, but Topical 1% luliconazole proved

to be every effective in therapeutically when compared with the 1% terbinafine cream.

ANALYSIS OF RESULTS AT END OF FOURTH WEEK

The reduction in the mean pruritis score (Mean rank = 28.5), mean erythema score (mean rank= 27.5), mean scaling score (Mean rank = 27) showed a statistically significant difference with a P value (≤0.05) was obtained in the terbinafine as well as in the luliconazole group. But the mean rank was lower than that obtained at the end of 1st week.

Eventhough both the drug were effective in providing therapeutic response. Topical luliconazole proved to be every effective in therapeutic response from the results analyzed in the group effects.

The percentage reduction in mean composite score from baseline to 1st week are 59% and 72% in terbinafine group and luliconazole group respectively at the end of 1st week. At the end of 2nd week the reduction is 86% and 91% in terbinafine group and luliconazole group respectively.

At the end of 4th week the reduction is 89% and 93% in terbinafine group and luliconazole group respectively. Effective reduction in the percentage of mean composite score is seen in luliconazole group than that of terbinafine. When compared to 2nd and 4th week effective response is seen in 1st week.

Comparisons of lab investigations of KOH study between terbinafine and luliconazole groups shows, fungal elements are positive at baseline in all the 60 patients in each group. After 1st week of therapy, fungal elements were absent in

61 % of patient in terbinafine group and in 86% of patients in luliconazole group. This is statistically significant with a P value (P = <0.005). After 2nd week of therapy, in KOH results fungal hyphae were absent in 95% and 96 % in terbinafine group & luliconazole group respectively with a P value 0.364 and at the end of 4th week, 95% fungal hyphae were absent in terbinafine group and 100% in luliconazole group.

Comparisons of mycological culture results of terbinafine and luliconazole groups showed 67% & 88 % culture negative (P < 0.05) after completing the therapy for a period of 1st week, A statistically significant difference is noted at 1st week. At the end of 2nd week and 4th week 96% and 100% were culture negative with P=0.495, 0.208 with no statistically significant difference.

SAFETY ANALYSIS OF THE TWO DRUGS:

Three patients in TBF group experienced burning sensation (2), and mild contact dermatitis (1) and two patients in LLCZ group reported contact dermatitis but the occurrence of adverse effects did not require discontinuation of therapy.

7. SUMMARY

This study is an open labelled randomized comparative study of topical 1 % terbinafine with 1% luliconazole applied once daily in patients of Tinea corporis and Tinea cruris. Patients who have fulfilled the selection criteria were randomized into 2 groups as Group A (1% Terbinafine) and Group B (1% LLCZ) applied once daily for two weeks. A total of 120 patients were involved in this study. In this 113 patients were completed the study and 7 patients were dropped out of the study.

The parameters like clinical improvement, KOH results and culture were followed up. The results indicated that one week of treatment with 1 % LLCZ is sufficient in the treatment of tinea corporis and tinea cruris infection. It is inferred that high effectiveness is seen with shorter duration of therapy with 1% LLCZ. It has potent antifungal activity against dermatophytes.

The results indicate the 1% LLCZ cream is sufficiently effective for short term therapy than Terbinafine in treating Tinea corporis and Tinea cruris. There were no serious adverse events observed in the study period.

Inspite of many excellent anti-fungal agents availability therapy of dermatophytosis require regular topical application for a longer period of time to provide therapeutic effect and it may impair patient's compliance resulting in recurrences LLCZ having an effective antifungal activity within a shorter period of time improved the patient's compliance and helping preventing recurrences

8. CONCLUSION

From this study, it is concluded that therapy with 1 % Luliconazole cream applied once daily for 2 weeks is found to be more efficacious than 1 % Terbinafine for 2 weeks applied daily in the treatment of patients with tinea corporis and tinea cruris. This is evidenced by marked improvement in the clinical scoring and the statistically significant difference in the mean composite score between the two groups. Majority of the patients (72%) receiving 1 % LLCZ cream achieved resolution of symptoms within the **first week** of therapy than terbinafine group (59%). The reduction in symptoms were higher (91%) in the 1 % LLCZ cream group at the end of 2nd week also. LLCZ is capable of producing marked improvement in clinical signs and symptoms as well as eradicating the fungi effectively and this effect is evident in half of the treatment time required for 1 % terbinafine. The treatment related side effects were also minimal for both the groups. Hence topical 1 % LLCZ cream seems to be a promising medication in treating tinea corporis & tinea cruris in its better therapeutic efficacy as well as safety aspects than 1% terbinafine cream.

LIMITATIONS OF THE STUDY

- The effectiveness of the two study drugs TBF 1% cream and LLCZ1% was not compared in other variants of tinea infections.
- Effectiveness was not assessed in immunocompromised patients who are more prone to have tinea infections.

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ABBREVIATIONS

AMB – Amphotericin B

CYP2D6 – Cytochrome 2 D 6

C (max) – Maximum concentration

E. floccosum - Epidermophyton floccosum

5- FC – 5 Flucytosine

IFN alpha – Interferon alpha

IL-1 – Interleukins

LLCZ – Luliconazole

M. canis – Microsporum canis

TNF alpha – Tumor necrosis factor alpha

T. rubrum – Trichophyton rubrum

T. Mentagrophytes – Trichophyton mentagrophytes

T. capitis – Tinea capitis

T.barbae – Tinea barbae

T.unguim – Tinea unguim

TBF- Terbinafine

T1 – Time interval from baseline to first week

T2 – Time interval from baseline to second week

T3 – Time interval from baseline to fourth week

CHENGALPATTU MEDICAL COLLEGE, CHENGALPATTU

Title of Work	:	**A prospective, randomized,open label study to compare the Efficacy of topical luliconazole with topical terbinafine in the Treatment of tinea corporis and tinea cruris.**
Principal Investigator	:	Dr.G.Amudha
Designation	:	1st Year MD Pharmacology
Co-Investigators	:	1.Dr.B.Sharmila,MD Asso.Professor Department of Pharmacology. 2.Dr.O.H.Hema,Md HOD Dept. of the Dermatology 3.Dr.K.Baskaran,MD HOD,Dept. of Pharmacology 4.Dr.A.Vijayalakshmi,MD HOD, Dept. of Microbiology
Department	:	Pharmacology

The request for an approval From the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 29.02.2016 at the Medical Education Unit, Government Chengalpattu Medical College, Chengalpattu at 11.00 PM.

The Members of the committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal Investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of any changes in study procedure, site, investigator investigation or guide or any other changes.
2. You should not deviate from the area of work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
4. You should abide to the rules and regulations of the institution(s).
5. You should complete the work within the specific period and if any extension is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on complete of work.

MEMBER SECRETARY,
IEC, CHENGALPATTU MEDICAL COLLEGE
CHENGALPATTU.

DEAN
CHENGALPATTU MEDICAL COLLEGE
CHENGALPATTU.

INFORMATION SHEET

We are conducting a study on "**A PROSPECTIVE, RANDOMIZED OPEN LABEL STUDY TO COMPARE THE EFFICACY OF TOPICAL LULICONAZOLE WITH TOPICAL TERBINAFINE IN THE TREATMENT OF TINEA CORPORIS AND TINEA CRURIS"** in Chengalpattu Medical College Hospital, Chengalpattu.

For this your participation may be of immense value.

We are selecting patients who satisfy our inclusion criteria are included in the study.

The privacy of the patients will be maintained throughout the study, in the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Participation depends on patients own voluntary decision. Their decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature of the Participant

Dr.G.Amudha.

Date :

Place :

Information to participants

Principal Investigator :- Dr.G.Amudha

MD Pharmacology , Postgraduate

Chengalpattu medical College

Chengalpattu.

Name of the participant :-

_____

Title : "A Prospective, Open Label, Randomized,Study To Compare The Efficacy Of Topical Luliconazole With Topical Terbinafine In The Treatment Of Tinea Corporis And Tinea Cruris."

This study is conducted in our institution, Chengalpattu medical College, Chengalpattu.

You are invited to take part in this study. The information in this document is meant to help you to decide whether or not to take part. Please feel free to able if you have any queries or concerns.

You are being asked to participate in this study conducted in the department of Medicine and department of pharmacology, Chengalpattu Medical College.

Purpose of research :

Comparing the efficacy of topical luliconazole with topical terbinafine in the treatment of tinea corporis and tinea cruris to shorten the duration of treatment and prevention of relapses with better therapy.

The study is conducted with permission from the Institutional ethical committee.

Study design : A prospective, open label, randomized, comparitive study.

Study Procedure:

Patients who fulfilled the selection criteria will be recruited for the study. After getting informed consent, patients will be randomly allotted to either group A (luliconazole 1%topical cream once daily at bed time for 2 weeks) or group B(terbinafine1% topical cream once daily at bed time for 2 weeks).

Complete history, clinical examination as per the proforma attached, and baseline lab investigations will be taken at the beginning of the study.

Clinical signs and symptoms (pruritus,erythema,scaling) are assessed using the 4-point scale.KOH positive results for fungal elements are considered for enrollement.Mycological screening test(KOH mount) as well as the clinical scoring are performed at base line,at day 7, at day 14(at the end of treatment),and at day42(follow up phase). Fungal culture was also done at baseline, at day 14 and at day 42. Complete clearance and Effective treatment are assessed

You may have to come to hospital for examination and investigations apart from your scheduled visits if required.

You must not participate if you are pregnant, breast feeding a child or suffering from any serious medical illness like diabetes, kidney or liver disease, cancer or any surgical illness.

Benefits of the study;

The results of the research may provide benefits to the society in term of recent therapeutic advancements and shorter duration of treatment in superficial fungal infections.

தகவல் படிவம்

செங்கல்பட்டு அரசு பொது மருத்துவமனையில் படர் தாமரை என்னும் பூஞ்சை தொற்று நோய்க்கு தோல் சிகிச்சைப்பிரிவில் வழங்கப்படும் லுலிகொனசொல் மேற்பூச்சு மருந்து மற்றும் டெர்பினஃபின் மேற்பூச்சு மருந்து ஆகியவற்றின் பயன்பாடு குறித்தான ஒப்பீட்டு ஆய்வு மேற்கொள்ளப்படுகிறது.

- இந்த ஆய்வு மருத்துவர் கோ.அமுதா அவர்கலால் அனுபவம் வாய்ந்த மருத்துவர்களின் உதவியோடு நடத்தப்படுகிறது.

- இம்மருந்துகள் அனுதின பயன்பாட்டில் உள்ள மருந்துகளே. இம்மருந்துகளினால் மிகப் பெரிய அளவில் பக்க விளைவுகள் ஏற்பட வாய்ப்புகள் இல்லை.

- இந்த ஆய்வின் போது ஒரு பிரிவினருக்கு லுலிகொனசொல் மேற்பூச்சு மருந்தும் மற்றொரு பிரிவினருக்கு டெர்பினஃபின் மேற்பூச்சு மருந்தும் வழங்கப்படும்.

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- இந்த ஆய்வின் தொடக்கத்திலும் முடிவிலும் இரத்தப் பரிசோதனை மற்றும் பூஞ்சை கண்டறியும் சோதனைகள் செய்யப்படும்.

- நோயின் தன்மைகளை வெளியிடும்போது தங்களது பெயரையோ, அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

- இந்த ஆய்வில் பங்கேற்பது உங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆய்விலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

- இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

நாள்:

இடம்: கையொப்பம்

CONSENT FORM

(This is only a guideline –Relevant changes to be made as per the study requirements)

Title of the study : **"A PROSPECTIVE, RANDOMIZED OPEN LABEL STUDY TO COMPARE THE EFFICACY OF TOPICAL LULICONAZOLE WITH TOPICAL TERBINAFINE IN THE TREATMENT OF TINEA CORPORIS AND TINEA CRURIS."**

Name of the participant :_____

Name of the Investigator : Dr.G.Amudha

Name of the Institution : Chengalpattu Medical College Hospital

Documentation of the informed consent.

I _____have read the information in this form (or it has been read to me).I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in **"A PROSPECTIVE, RANDOMIZED OPEN LABEL STUDY TO COMPARE THE EFFICACY OF TOPICAL LULICONAZOLE WITH TOPICAL TERBINAFINE IN THE TREATMENT OF TINEA CORPORIS AND TINEA CRURIS".**

1. I have read and understand this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past_____including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
8. I have not participated in any research study within the past_____.
9. I have not donated blood within the past_____- Add if the study involves extensive blood sampling.
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
11. I am also aware that the investigator may treatment my participated in the study at any time for any reason, without my consent.
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt.Agencies, and IEC. I understand that they are publicly presented.
13. I have understood that my identity will be kept confidential if my data are publicly presented.
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the Investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature/thumb impression of the participant (or legal representative if participant incompetent)

Name_____signature_____Date_____

Name and signature of impartial witness (require for illiterate patients)

Name_____signature_____Date_____

Address and contact number of the impartial witness:

_____

Name and signature of the investigator or his representative obtaining consent:

Name_____signature_____Date_____

_____

Name and signature of the investigator or his representative obtaining consent:

Name_____signature_____Date_____

NOTE:-

For observational studies in nature or those in which only patient's tissue, body fluids are collected for any kind of analysis the following elements in the patient information leaflet will need be included – background of the study the purpose for which the sample will be used: confidentially of data are right to refuse to give specimens should be included.

Points 6, 7,8,9,10,11 of consent document may be excluded in such cases.

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு: செங்கல்பட்டு அரசு பொது மருத்துவமனையில் படர் தாமரை என்னும் பூஞ்சை தொற்று நோய்க்கு தோல் சிகிச்சைப்பிரிவில் வழங்கப்படும் லுலிகொனசொல் மேற்பூச்சு மருந்து மற்றும் டெர்பினஃபின் மேற்பூச்சு மருந்து ஆகியவற்றின் பயன்பாடு குறித்தான ஒப்பீட்டு ஆய்வு.

இடம்: **பெயர்:**

கையொப்பம்:

தேதி:

திரு/திருமதி _____

_____

என்ற விலாசத்தில் வசிக்கும் நான், எனக்கு அளிக்கப்பட்ட தகவல் படிவத்தில் உள்ள விஷயங்களைப் படித்தும் கேட்டும் புரிந்து கொண்டேன்.

இந்த ஆய்விற்குத் தேவையான இரத்தப் பரிசோதனை, பூஞ்சை பரிசோதனைகளுக்கு உட்பட சம்மதிக்கிறேன்.

இந்த ஆய்வில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன்.

ஆய்வில் தொடர்ந்து பங்குபெற விருப்பம் இல்லை என்றால் விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

ஆய்வின் முடிவினை சொந்த அடையாளங்களை வெளியிடாமல் மருத்துவ ஆராய்ச்சிக்காக பயன்படுத்திக் கொள்ள சம்மதிக்கிறேன்.

நாள்:

இடம்: **கையொப்பம்**

PROFORMA

Serial No:

Name: **Hospital No:**

- **Age:** **Sex: a: male b: female**
- Present History:

  Time of onset of disease:

  Duration:
- Past History :
- History Of Use Of any other drugs :
- History Of similar lesions in family members:
- General Examination:

  Heart rate :

  Blood Pressure :

  Respiratory Rate :
- Local examination:

  Site of lesion:

  Size of lesion:
- Assessment of clinical signs and symptoms

4 Point Scale for assessing

Pruritus : None = 0,Mild = 1,Moderate = 2,Severe = 3

Erythema: None = 0,Mild = 1,Moderate = 2,Severe = 3

Scaling : None = 0,Mild = 1,Moderate = 2,Severe = 3

Severity scoring is done as follows:

Clinical signs and symptoms	Baseline	At the end 1st week	At the end of 2nd week	At the end of 4th week
1.Erythema				
2.Scaling				
3.Pruritus				
Total Score				

Systemic Examination

- CVS :
- RS :
- Abdomen :
- CNS :

Lab investigations

Investigations	**Base line**	**1st week**	**2nd week**	**4th week**
KOH mount				
Fungal culture				

MASTER CHART

									pruritus	erythema	scaling	composite	pruritus	erythema	scaling	composite	pruritus	erythema	scaling	composite	pruritur	erythema	scaling	composite score	composite	composite	composite	composite score	KOH BL	KOH 1	KOH 2	KOH 4		Fungal culture		
S.no	Groups	Age	sex	Duration	Relationship to climate	Contact history	Family history	Disease	baseline	baseline	baseline	baseline	end of 1st week	1st week	1st week	1st week	2wk	2wk	2wk	2nd week	4wk	4wk	4wk	4th week	baseline	1st week	2nd week	4th week					FCB	FC1	FC2	FC4
1	1	36	F	15	Yes	No	No	TINEA CORPORIS	2	3	1	6	0	1	0	1	0	1	0	1	0	1	0	1	6	1	1	1	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
2	1	55	M	14	No	No	No	TINEA CORPORIS	2	2	2	6	2	0	1	3	0	0	0	0	0	0	0	0	6	3	0	0	Positive	Positive	Negative	Negative	E.floccosum	Negative	Negative	Negative
3	1	33	F	14	No	Yes	Yes	TINEA CORPORIS	2	2	2	6	1	1	2	4	1	0	0	1	1	1	0	2	6	4	1	1	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
4	1	58	M	21	Yes	No	No	TINEA CORPORIS	2	3	3	8	1	2	1	4	1	1	0	2	0	0	0	0	8	4	2	2	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
5	1	22	M	21	No	No	No	TINEA CORPORIS	2	2	2	6	1	1	0	2	0	0	0	0	0	0	0	0	6	2	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
6	1	32	M	20	No	No	No	TINEA CORPORIS	1	2	1	4	1	1	0	2	0	0	0	0	0	0	0	0	4	2	0	0	Positive	Negative	Negative	Negative	T.RubrumT.Rubrun	Negative	Negative	Negative
7	1	21	M	14	Yes	Yes	Yes	TINEA CRURIS	3	2	2	7	1	1	1	3	0	1	1	2	0	1	0	1	7	3	2	1	Positive	Positive	Positive	Positive	T.Mentagrophyte	Positive	Positive	Positive
8	1	31	M	15	No	No	Yes	TINEA CORPORIS	2	2	1	5	2	1	0	3	1	0	0	1	0	0	0	0	5	3	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
9	1	20	M	15	Yes	No	No	TINEA CORPORIS	2	2	2	6	1	1	1	3	0	1	0	1	0	1	0	1	6	3	1	1	Positive	Positive	Negative	Negative	T.Rubrum	Negative	Negative	Negative
10	1	26	F	20	No	No	No	TINEA CORPORIS	2	2	2	6	2	0	0	2	0	0	0	0	0	0	0	0	6	2	0	0	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
11	1	26	M	14	No	No	No	TINEA CORPORIS	1	1	1	3	1	1	0	2	0	0	0	0	0	0	0	0	3	2	0	0	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
12	1	45	M	21	Yes	No	No	TINEA CRURIS	2	3	3	8	1	3	2	6	0	0	0	0	0	0	0	0	8	6	0	0	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
13	1	49	M	14	No	No	No	TINEA CORPORIS	2	2	1	5	2	1	1	4	1	0	0	1	1	0	0	1	5	4	1	1	Positive	Positive	Negative	Negative	T.Mentagrophytes	Positive	Negative	Negative
14	1	23	M	15	No	No	No	TINEA CRURIS	2	1	2	5	0	0	1	1	0	0	1	1	0	0	1	1	5	1	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
15	1	26	M	10	Yes	no	no	TINEA CORPORIS	2	2	1	5	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
16	1	36	M	9	Yes	No	No	TINEA CORPORIS	2	2	1	5	2	1	0	3	1	0	0	1	1	0	0	1	5	3	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
17	1	43	M	10	No	No	No	tinea cruris	3	3	2	8	0	2	1	3	0	1	0	1	0	1	0	1	8	3	1	1	Positive	Positive	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
18	1	19	M	18	No	Yes	Yes	TINEA CORPORIS	2	2	1	5	1	0	1	2	1	0	0	1	1	0	0	1	5	2	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
19	1	35	M	15	No	No	No	TINEA CORPORIS	1	1	1	3	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
20	1	19	F	15	Yes	yes	yes	tinea cruris	3	3	3	9	2	1	1	4	1	1	0	2	1	1	0	2	9	4	2	2	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
21	1	46	M	10	No	No	No	TINEA CORPORIS	2	2	2	6	0	1	2	3	0	0	1	1	0	0	1	1	6	3	1	1	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
22	1	35	M	24	No	No	No	tinea cruris	1	1	2	4	0	0	1	1	0	0	0	0	0	0	0	0	4	1	0	0	Positive	Negative	Negative	Negative	E.floccosum	Negative	Negative	Negative
23	1	19	M	23	No	No	No	TINEA CORPORIS	3	2	2	7	2	1	0	3	0	1	0	1	0	1	0	1	7	3	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
24	1	51	M	17	No	No	No	TINEA CRURIS	2	2	2	6	0	1	0	1	0	0	0	0	0	0	0	0	6	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
25	1	22	F	12	Yes	No	No	TINEA CRURIS	3	3	2	8	1	0	1	2	0	0	0	0	0	0	0	0	8	2	0	0	Positive	Positive	Negative	Negative	T.Mentagrophytes	Positive	Negative	Negative
26	1	20	F	17	Yes	Yes	Yes	TINEA CRURIS	2	2	3	7	1	1	1	3	1	0	0	1	1	0	0	1	7	3	1	1	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
27	1	52	M	18	No	No	No	TINEA CORPORIS	2	2	1	5	1	1	1	3	0	1	0	1	0	1	0	1	5	3	1	1	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
28	1	18	M	10	No	No	No	TINEA CORPORIS	3	2	2	7	1	1	0	2	0	0	0	0	0	0	0	0	7	2	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
29	1	24	M	10	No	No	No	TINEA CORPORIS	2	3	1	6	1	1	0	2	0	1	0	1	0	1	0	1	6	2	1	1	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
30	1	30	F	23	No	No	No	TINEA CRURIS	2	2	2	6	0	1	1	2	0	0	0	0	0	0	0	0	6	2	0	0	Positive	Positive	Negative	Negative	T.Rubrum	Negative	Negative	Negative
31	1	22	F	16	No	No	No	TINEA CORPORIS	2	2	2	6	2	0	1	3	0	0	1	1	0	0	0	0	6	3	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
32	1	28	M	12	No	No	No	TINEA CRURIS	2	1	1	4	0	1	0	1	0	0	0	0	0	0	0	0	4	1	0	0	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
33	1	33	F	25	No	No	No	TINEA CORPORIS	2	2	2	6	1	1	0	2	1	0	0	1	0	0	0	0	6	2	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
34	1	24	M	22	Yes	No	No	TINEA CORPORIS	3	2	2	7	1	0	1	2	0	0	1	1	0	0	1	1	7	2	1	1	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
35	1	36	F	11	No	No	No	TINEA CORPORIS	2	2	2	6	0	1	1	2	0	1	0	1	0	1	0	1	6	2	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
36	1	21	M	16	No	Yes	Yes	TINEA CRURIS	2	1	1	4	2	0	0	2	1	0	0	1	0	0	0	1	4	2	1	1	Positive	Negative	Negative	Negative	Mentagrophytesubr	Negative	Negative	Negative
37	1	55	F	15	No	No	No	TINEA CORPORIS	2	3	2	7	1	1	1	3	1	0	0	1	0	0	0	0	7	3	1	0	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
38	1	36	M	16	No	No	No	TINEA CORPORIS	2	1	1	4	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
39	1	22	F	22	No	Yes	Yes	TINEA CORPORIS	2	2	2	6	1	1	1	3	1	0	1	2	0	0	1	1	6	3	2	2	Positive	Negative	Negative	Negative	T.RubrumT.Rubrur	Negative	Negative	Negative
40	1	34	F	10	Yes	No	No	TINEA CORPORIS	1	2	2	5	0	2	1	3	0	0	0	0	0	0	0	0	5	3	0	0	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
41	1	21	F	12	Yes	No	No	TINEA CORPORIS	2	1	2	5	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
42	1	40	M	24	No	No	No	TINEA CRURIS	3	2	2	7	1	1	0	2	1	0	0	1	1	0	0	1	7	2	1	1	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
43	1	62	F	17	No	No	No	TINEA CORPORIS	2	2	1	5	2	1	0	3	0	1	0	1	0	1	0	1	5	3	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
44	1	41	M	12	No	No	No	TINEA CRURIS	1	2	2	5	0	1	2	3	0	0	0	0	0	0	0	0	5	3	0	0	Positive	Positive	Negative	Negative	E.floccosum	Positive	Negative	Negative
45	1	21	M	18	No	No	No	TINEA CORPORIS	2	1	1	4	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
46	1	39	F	23	No	No	No	TINEA CORPORIS	2	3	2	7	2	1	1	4	1	1	1	3	1	1	1	3	7	4	3	2	Positive	Positive	Positive	Positive	T.Rubrum	Positive	Positive	Positive
47	1	19	F	17	No	No	No	TINEA CORPORIS	1	1	1	3	1	1	0	2	0	0	0		0	0	0	0	3	2	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative

									pruritus	erythema	scaling	composite	pruritus	erythema	scaling	composite	pruritus	erythema	scaling	composite	pruritur	erythema	scaling	composite score	composite	composite	composite	composite score	KOH BL	KOH 1	KOH 2	KOH 4		Fungal culture		
S.no	Groups	Age	sex	Duration	Relationship to climate	Contact history	Family history	Disease	baseline	baseline	baseline	baseline	end of 1st week	1st week	1st week	1st week	2wk	2wk	2wk	2nd week	4wk	4wk	4wk	4th week	baseline	1st week	2nd week	4th week					FCB	FC1	FC2	FC4
48	1	40	F	15	No	No	No	TINEA CORPORIS	2	2	2	6	2	0	0	2	1	0	0	1	0	0	0	0	6	2	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
49	1	51	M	16	No	No	No	TINEA CORPORIS	2	1	1	4	1	0	0	1	1	0	0	1	0	0	0	0	4	1	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
50	1	31	M	18	No	No	No	TINEA CRURIS	2	1	1	4	0	1	1	2	0	0	0	0	0	0	0	0	4	2	0	0	Positive	Positive	Negative	Negative	T.Mentagrophytes	Positive	Negative	Negative
51	1	39	F	17	No	No	No	TINEA CORPORIS	2	2	1	5	1	1	0	2	0	1	0	1	0	1	0	1	5	2	1	1	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
52	1	23	F	22	No	No	No	TINEA CRURIS	3	2	2	7	1	1	1	3	0	1	1	2	0	0	1	1	7	3	2	1	Positive	Positive	Positive	Positive	T.Rubrum	Positive	Positive	Positive
53	1	23	M	20	No	No	No	TINEA CORPORIS	2	2	1	5	0	1	1	2	0	1	1	2	0	0	1	1	5	2	2	2	Positive	Negative	Negative	Negative	T.Mentagrophytes	Negative	Negative	Negative
54	1	34	F	16	Yes	No	No	TINEA CRURIS	2	3	2	7	2	2	0	4	1	1	0	2	1	1	0	2	7	4	2	2	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
55	1	27	M	15	No	Yes	Yes	TINEA CRURIS	2	3	3	8	2	1	1	4	1	1	0	2	1	1	0	2	8	4	2	1	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
56	1	18	M	18	No	No	No	TINEA CRURIS	2	2	2	6	0	1	1	2	0	0	1	1	0	0	1	1	6	2	1	1	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
57	2	19	M	15	No	No	No	TINEA CORPORIS	2	2	2	6	1	1	1	3	1	1	0	2	1	1	0	2	6	3	2	2	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
58	2	29	F	20	No	No	Yes	TINEA CORPORIS	1	3	3	7	1	1	0	2	0	1	0	1	0	1	0	1	7	2	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
59	2	19	F	18	Yes	Yes	Yes	TINEA CRURIS	2	2	2	6	0	0	1	1	0	0	0	0	0	0	0	0	6	1	0	0	Positive	Negative	Negative	Negative	E.floccosum	Negative	Negative	Negative
60	2	37	F	18	No	No	Yes	TINEA CORPORIS	2	2	2	6	0	1	0	1	0	0	0	0	0	0	0	0	6	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
61	2	30	F	14	No	No	Yes	TINEA CORPORIS	3	2	3	8	1	1	0	2	1	0	0	1	0	0	0	0	8	2	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
62	2	54	M	15	No	Yes	No	TINEA CORPORIS	2	2	2	6	0	0	1	1	0	0	1	1	0	0	1	1	6	1	1	1	Positive	Negative	Negative	Negative	E.Floccosum	Negative	Negative	Negative
63	2	31	F	17	Yes	No	No	TINEA CORPORIS	2	1	1	4	1	1	0	2	0	0	0	0	0	0	0	0	4	2	0	0	Positive	Positive	Negative	Negative	E.Foccosum	Positive	Negative	Negative
64	2	22	M	18	No	No	Yes	TINEA CRURIS	3	2	2	7	1	1	1	3	0	1	1	2	0	0	1	1	7	3	2	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
65	2	25	M	20	Yes	No	No	TINEA CRURIS	2	1	1	4	2	0	0	2	0	0	0	0	0	0	0	0	4	2	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
66	2	30	F	17	No	No	No	TINEA CORPORIS	2	3	2	7	1	1	1	3	0	0	1	1	0	0	1	1	7	3	2	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
67	2	51	M	16	No	No	No	TINEA CORPORIS	2	2	2	6	1	0	1	2	0	0	0	0	0	0	0	0	6	2	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
68	2	55	F	17	No	No	No	TINEA CRURIS	2	2	0	4	0	1	0	1	0	0	0	0	0	0	0	0	4	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
69	2	29	M	14	No	No	No	TINEA CRURIS	2	3	2	7	0	1	0	1	0	0	0	0	0	0	0	0	7	1	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
70	2	37	M	18	No	No	No	TINEA CORPORIS	1	2	1	4	1	1	0	2	0	1	0	1	0	1	0	1	4	2	1	1	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
71	2	36	M	14	No	No	No	TINEA CORPORIS	2	2	0	4	2	2	0	4	0	0	0	0	0	0	0	0	4	4	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
72	2	40	F	21	No	No	No	TINEA CRURIS	2	1	1	4	0	0	1	1	0	0	1	1	0	0	1	1	4	1	1	1	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
73	2	52	F	14	Yes	No	No	TINEA CRURIS	2	3	2	7	0	1	0	1	0	0	0	0	0	0	0	0	7	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
74	2	30	M	16	No	Yes	No	TINEA CORPORIS	1	1	1	3	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
75	2	55	F	18	No	No	No	TINEA CORPORIS	2	3	3	8	1	0	1	2	1	0	0	1	0	0	0	0	8	2	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
76	2	22	M	18	No	No	Yes	TINEA CORPORIS	3	2	2	7	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
77	2	20	M	15	No	No	No	TINEA CRURIS	2	2	2	6	0	1	1	2	0	0	0	0	0	0	0	0	6	2	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
78	2	43	F	15	Yes	No	No	TINEA CORPORIS	3	2	2	7	2	0	0	2	0	0	0	0	0	0	0	0	7	2	0	0	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
79	2	50	F	21	No	No	No	TINEA CRURIS	2	2	1	5	2	1	0	3	0	0	0	0	0	0	0	0	5	3	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
80	2	30	M	16	No	No	No	TINEA CORPORIS	3	2	2	7	0	0	1	1	0	0	1	1	0	0	1	1	7	1	1	1	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
81	2	51	M	14	No	No	No	TINEA CORPORIS	2	2	2	6	0	1	0	1	0	0	0	0	0	0	0	0	6	1	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Positive	Negative	Negative
82	2	45	F	20	No	No	No	TINEA CRURIS	1	1	1	3	1	0	0	1	0	0	0	0	0	0	0	0	3	1	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
83	2	54	M	14	No	No	No	TINEA CORPORIS	2	2	2	6	2	1	0	3	1	0	0	1	0	0	0	0	6	3	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
84	2	21	F	14	No	No	No	TINEA CRURIS	3	3	3	9	1	0	0	1	0	0	0	0	0	0	0	0	9	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
85	2	33	F	14	Yes	Yes	No	TINEA CORPORIS	1	2	2	5	0	1	0	1	0	0	0	0	0	0	0	0	5	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
86	2	20	M	21	Yes	No	No	TINEA CORPORIS	1	0	2	3	1	0	1	2	0	0	1	1	1	0	0	1	3	2	2	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
87	2	32	F	15	No	No	Yes	TINEA CORPORIS	2	2	2	6	1	1	0	2	1	0	0	1	0	0	0	0	6	2	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
88	2	37	F	15	No	No	No	TINEA CORPORIS	2	1	1	4	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
89	2	47	M	15	No	No	No	TINEA CORPORIS	3	2	2	7	1	0	1	2	0	0	1	1	0	0	0	0	7	2	1	0	Positive	Positive	Negative	Negative	T.Rubrum	Negative	Negative	Negative
90	2	29	M	21	No	No	No	TINEA CRURIS	2	2	2	6	0	1	1	2	0	0	0	0	0	0	0	0	6	2	0	0	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
91	2	59	M	16	No	No	No	TINEA CORPORIS	1	1	1	3	0	1	0	1	0	0	0	0	0	0	0	0	3	1	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
92	2	52	F	21	Yes	No	No	TINEA CORPORIS	2	3	2	7	1	0	0	1	1	0	0	1	1	0	0	1	7	1	1	1	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
93	2	25	M	15	No	No	No	TINEA CORPORIS	1	0	1	2	0	0	1	1	0	0	0	0	0	0	0	0	2	1	0	0	Positive	Positive	Negative	Negative	T.Rubrum	Positive	Negative	Negative
94	2	23	F	18	Yes	No	No	TINEA CRURIS	2	3	2	7	1	0	1	2	0	0	1	1	0	0	1	1	7	2	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative

									pruritus	erythema	scaling	composite	pruritus	erythema	scaling	composite	pruritus	erythema	scaling	composite	pruritur	erythema	scaling	composite score	composite	composite	composite	composite score	KOH BL	KOH 1	KOH 2	KOH 4		Fungal culture		
S.no	Groups	Age	sex	Duration	Relationship to climate	Contact history	Family history	Disease	baseline	baseline	baseline	baseline	end of 1st week	1st week	1st week	1st week	2wk	2wk	2wk	2nd week	4wk	4wk	4wk	4th week	baseline	1st week	2nd week	4th week					FCB	FC1	FC2	FC4
95	2	35	M	17	No	No	No	TINEA CORPORIS	3	2	3	8	0	1	0	1	0	1	0	1	0	1	0	1	8	1	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
96	2	35	M	16	No	No	No	TINEA CRURIS	2	2	2	6	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	Positive	Positive	Negative	Negative	T.Rubrum	Negative	Negative	Negative
97	2	27	M	20	No	No	No	TINEA CRURIS	3	3	3	9	1	1	0	2	0	1	0	1	0	1	0	1	9	2	1	1	Positive	Negative	Negative	Negative	T.Mentagrophyte	Negative	Negative	Negative
98	2	47	F	14	Yes	No	No	TINEA CORPORIS	2	1	1	4	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
99	2	38	F	16	No	No	No	TINEA CORPORIS	2	3	1	6	1	1	0	2	1	0	0	1	1	0	0	1	6	2	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Negative	Negative	Negative
100	2	18	F	7	No	No	No	TINEA CORPORIS	2	2	1	5	0	2	1	3	0	1	0	1	0	1	0	1	5	3	1	1	Positive	Negative	Negative	Negative	T.Rubrum	Mentagrophy	Negative	Negative
101	2	42	F	10	No	No	No	TINEA CORPORIS	2	2	1	5	0	1	1	2	0	0	0	0	0	0	0	0	5	2	0	0	Positive	Positive	Negative	Negative	T.Rubrum	T.Rubrum	Negative	Negative
102	2	26	F	12	Yes	No	No	TINEA CORPORIS	1	2	2	5	1	1	0	2	0	0	0	0	0	0	0	0	5	2	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	T.Rubrum	Negative	Negative
103	2	28	F	9	No	Yes	No	TINEA CRURIS	2	2	2	6	0	0	2	2	0	0	0	0	0	0	0	0	6	2	0	0	Positive	Positive	Negative	Negative	T.Rubrum	T.Rubrum	Positive	Negative
104	2	35	M	51	No	Yes	No	TINEA CORPORIS	2	1	1	4	0	1	0	1	0	0	0	0	0	0	0	0	4	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	Mentagrophy	Negative	Negative
105	2	19	M	21	No	No	No	TINEA CRURIS	2	1	0	3	1	1	0	2	0	0	0	0	0	0	0	0	3	2	0	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	Mentagrophy	Negative	Negative
106	2	41	F	15	Yes	Yes	No	TINEA CRURIS	1	0	1	2	1	0	1	2	1	0	0	1	0	0	0	0	2	2	1	0	Positive	Positive	Negative	Negative	T.Mentagrophyte	ubrumT.Rub	Positive	Negative
107	2	45	M	18	Yes	No	No	TINEA CORPORIS	2	1	2	5	0	1	0	1	0	0	0	0	0	0	0	0	5	1	0	0	Positive	Negative	Negative	Negative	T.Rubrum	T.Rubrum	Negative	Negative
108	2	21	M	17	No	No	No	TINEA CORPORIS	2	2	2	6	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	Positive	Negative	Negative	Negative	T.Rubrum	T.Rubrum	Negative	Negative
109	2	36	M	16	No	No	No	TINEA CORPORIS	1	2	2	5	0	0	2	2	0	0	1	1	0	0	0	0	5	2	1	0	Positive	Positive	Negative	Negative	T.Rubrum	T.Rubrum	Negative	Negative
110	2	60	M	20	Yes	No	No	TINEA CORPORIS	1	2	2	5	1	0	0	1	1	0	0	1	0	0	0	0	5	1	1	0	Positive	Negative	Negative	Negative	T.Rubrum	Mentagrophy	Negative	Negative
111	2	34	F	14	Yes	No	No	TINEA CORPORIS	2	3	2	7	1	1	0	2	0	1	0	1	0	0	0	0	7	2	1	0	Positive	Negative	Negative	Negative	T.Mentagrophyte	T.Rubrum	Negative	Negative
112	2	28	M	7	No	Yes	No	TINEA CRURIS	2	1	2	5	0	0	1	1	0	0	1	1	0	0	1	1	5	1	1	1	Positive	Negative	Negative	Negative	T.Rubrum	T.Rubrum	Negative	Negative
113	2	24	F	16	No	No	No	TINEA CORPORIS	2	3	2	7	1	0	1	2	0	0	1	1	0	0	0	0	7	2	1	0	Positive	Negative	Negative	Negative	T.Rubrum	T.Rubrum	Negative	Negative